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(54) Title: SECRETED PROTEINS AND USES THEREOF

(57) Abstract: The invention provides isolated nucleic acid molecules, designated TANGO 253, which encode proteins containing C1q domains and which are homologous to a human adipocyte complement-mediated protein precursor, TANGO 257, which encode proteins homologous to the human extracellular molecule olfactomedin, a molecule important in the maintenance, growth and differentiation of chemosensory cilia of olfactory neurons, INTERCEPT 258, which encode Ig domain-containing proteins that exhibit homology to an antigen (A33) expressed in colonic and small bowel epithelium, and TANGO 281, which encode proteins downregulated in megakaryocytes that fail to express the gata-1 transcription factor (a factor critical for blood cell formation) and can, therefore, represent direct or indirect gata-1 targets. The invention also provides antisense nucleic acid molecules, expression vectors containing the nucleic acid molecules of the invention, host cells into which the expression vectors have been introduced, and non-human transgenic animals in which a nucleic acid molecule of the invention has been introduced or disrupted. The invention still further provides isolated polypeptides, fusin polypeptides, antigenic peptides and antibodies. Diagnostic, screening and therapeutic methods utilizing compositions of the invention are also provided.

SECRETED PROTEINS AND USES THEREOF

This application is a continuation-in-part of U.S. patent application Serial No. 09/336,536, filed June 18, 2000, the contents of which are incorporated herein by reference in its entirety.

Background of the Invention

Many secreted proteins, for example, cytokines and cytokine receptors, play a vital role in the regulation of cell growth, cell differentiation, and a variety of specific cellular responses. A number of medically useful proteins, including erythropoietin, granulocyte-macrophage colony stimulating factor, human growth hormone, and various interleukins, are secreted proteins. Thus, an important goal in the design and development of new therapies is the identification and characterization of secreted and transmembrane proteins and the genes which encode them.

Many secreted proteins are receptors which bind a ligand and transduce an intracellular signal, leading to a variety of cellular responses. The identification and characterization of such a receptor enables one to identify both the ligands which bind to the receptor and the intracellular molecules and signal transduction pathways associated with the receptor, permitting one to identify or design modulators of receptor activity, *e.g.*, receptor agonists or antagonists and modulators of signal transduction.

Summary of the Invention

The present invention is based, at least in part, on the discovery of cDNA molecules which encode the TANGO 253, 257 and 281 proteins and the INTERCEPT 258 protein, all of which are either wholly secreted or transmembrane proteins.

The TANGO 253 proteins are C1q domain-containing polypeptides that exhibit homology to a human adipocyte complement-related protein precursor.

The TANGO 257 proteins are homologous to the human extracellular molecule olfactomedin, a molecule important in the maintenance, growth and differentiation of chemosensory cilia of olfactory neurons.

The INTERCEPT 258 proteins are Ig domain-containing polypeptides that exhibit homology to an antigen (A33) expressed in colonic and small bowel epithelium, a protein that may represent a cancer cell marker.

The TANGO 281 proteins represent proteins downregulated in megakaryocytes that fail to express the gata-1 transcription factor (a factor critical for blood cell formation) and can, therefore, represent direct or indirect gata-1 targets.

The TANGO 253, TANGO 257, INTERCEPT 258 and TANGO 281 proteins, fragments, derivatives, and variants thereof are collectively referred to herein as "polypeptides of the invention" or "proteins of the invention." Nucleic acid molecules encoding the polypeptides or proteins of the invention are collectively referred to as "nucleic acids of the invention."

The nucleic acids and polypeptides of the present invention are useful as modulating agents in regulating a variety of cellular processes. Accordingly, in one aspect, this invention provides isolated nucleic acid molecules encoding a polypeptide of the invention or a biologically active portion thereof. The present invention also provides nucleic acid molecules which are suitable for use as primers or hybridization probes for the detection of nucleic acids encoding a polypeptide of the invention.

The invention features nucleic acid molecules which are at least 30%, 35%, 40%, 45%, 50%, 55%, 65%, 75%, 85%, 95%, or 98% identical to the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:2, or the nucleotide sequence of the cDNA insert of an EpT253 clone deposited with ATCC® as Accession Number 207222, or a complement thereof.

The invention features nucleic acid molecules which are at least 30%, 35%, 40%, 45%, 50%, 55%, 65%, 75%, 85%, 95%, or 98% identical to the nucleotide sequence of SEQ ID NO:8, SEQ ID NO:9, or the nucleotide sequence of the cDNA insert of an EpTm253 clone deposited with ATCC® as Accession Number 207215, or a complement thereof.

The invention features nucleic acid molecules which are at least 95% or 98% identical to the nucleotide sequence of SEQ ID NO:15, SEQ ID NO:16, or the nucleotide sequence of the cDNA insert of an EpT257 clone deposited with ATCC® as Accession Number 207222, or a complement thereof.

The invention features nucleic acid molecules which are at least 95% or 98% identical to the nucleotide sequence of SEQ ID NO:21, SEQ ID NO:22, or the nucleotide sequence of the cDNA insert of an EpTm257 clone deposited with ATCC® as Accession Number 207217, or a complement thereof.

The invention features nucleic acid molecules which are at least 45%, 50%, 55%, 65%, 75%, 85%, 95%, or 98% identical to the nucleotide sequence of SEQ ID NO:26, SEQ ID NO:27, or the nucleotide sequence of the cDNA insert of an EpT258 clone deposited with ATCC® as Accession Number 207222, or a complement thereof.

The invention features nucleic acid molecules which are at least 45%, 50%, 55%, 65%, 75%, 85%, 95%, or 98% identical to the nucleotide sequence of SEQ ID NO:37, SEQ ID NO:38, or the nucleotide sequence of the cDNA insert of an EpTm258 clone deposited with ATCC® as Accession Number 207221, or a complement thereof.

The invention features nucleic acid molecules which are at least 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 75%, 85%, 95%, or 98% identical to the nucleotide sequence of SEQ ID NO:46, SEQ ID NO:47, or the nucleotide sequence of the cDNA insert of an EpT281 clone deposited with ATCC® as Accession Number 207222, or a complement thereof.

The invention features nucleic acid molecules which are at least 35%, 40%, 45%, 50%, 55%, 65%, 75%, 85%, 95%, or 98% identical to the nucleotide sequence of SEQ ID NO:56, SEQ ID NO:57, or the nucleotide sequence of the cDNA insert of an EpmT281 clone deposited with ATCC® as patent deposit Number PTA-224, or a complement thereof.

The invention features nucleic acid molecules which are at least 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 98% identical to the nucleotide sequence of SEQ ID NO: 1, 2, 8, 9, 15, 16, 21, 22, 26, 27, 37, 38, 46, 47, 56, 57, 77, 80, 91, 100, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191or 192, a complement thereof, or the non-coding strand of EpT 253, EpTm253, EpT257, EpTm257, EpT258, EpTm258, EpT281 or EpTm281 cDNA of ATCC® Accession 207222, Accession Number 207215, Accession 207217, Accession Number 207221, or patent deposit Number PTA-224, wherein said nucleic acid molecules encode polypeptides or proteins that exhibit at least one structural and/or functional feature of a polypeptide of the invention.

The invention features nucleic acid molecules of at least 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 1000, 1100, 1200 or 1300 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:1, the nucleotide sequence of an EpT253 cDNA of ATCC® Accession Number 207222, or a complement thereof.

The invention features nucleic acid molecules which include a fragment of at least 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700 or 720 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:2, or a complement thereof.

The invention features nucleic acid molecules which include a fragment of at least 540, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200 or 1250 contiguous

nucleotides of the nucleotide sequence of SEQ ID NO:8 the nucleotide sequence of an EpTm253 cDNa of ATCC® Accession Number 207215, or a complement thereof.

The invention features nucleic acid molecules of at least 310, 350, 400, 450, 500, 550, 600, 650 or 700 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:9, or a complement thereof.

The invention features nucleic acid molecules which include a fragment of at least 1800 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:15 or its complement.

The invention features nucleic acid molecules which include a fragment of at least 1150 or 1200 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:16, or its complement.

The invention features nucleic acid molecules which include a fragment of at least 1100, 1200, 1300, 1400, 1500, 1600 or 1700 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:21 the nucleotide sequence of an EpTm257 cDNA of ATCC® Accession Number 207217, or a complement thereof.

The invention features nucleic acid molecules which include a fragment of at least 1150 or 1200 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:22, or its complement.

The invention features nucleic acid molecules which include a fragment of at least 420, 450, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, or 1800 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:26 the nucleotide sequence of an EpT258 cDNA of ATCC® Accession Number 207222, or a complement thereof.

The invention features nucleic acid molecules which include a fragment of at least 50, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700 or 1800 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:27, or a complement thereof.

The invention features nucleic acid molecules which include a fragment of at least 675, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700 or 1800 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:37 the nucleotide sequence of an EpTm258 cDNA of ATCC® Accession Number 207221, or a complement thereof.

The invention features nucleic acid molecules which include a fragment of at least 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700 or 1800 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:38, or a complement thereof.

The invention features nucleic acid molecules which include a fragment of at least 50, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700 or 1800 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:46 the nucleotide sequence of an EpT281 cDNA of ATCC® Accession Number 207222, or a complement thereof.

The invention features nucleic acid molecules which include a fragment of at least 50, 100, 200, 300, 400, 500, 600, 700 or 750 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:47, or a complement thereof.

The invention features nucleic acid molecules which include a fragment of at least 550, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800 or 1850 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:56 the nucleotide sequence of an EpTm281 cDNA of ATCC® patent deposit Number PTA-224, or a complement thereof.

The invention features nucleic acid molecules which include a fragment of at least 50, 100, 200, 300, 400, 500, 600 or 700 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:57, or a complement thereof.

The invention features isolated nucleic acid molecules having a nucleotide sequence that is at least about 20, 50, 100, 150, 200, 250, 300, 400, 450, 500, 550, 600, 650, 700 or more contiguous nucleotides identical to the nucleic acid sequence of SEQ ID NOS: 1, 2, 8, 9, 15, 16, 21, 22, 26, 27, 37, 38, 46, 47, 56, 57, 77, 80, 91, 100, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191 or 192, or a complement thereof, or the non-coding strand of EpT253, EpTm253, EpT257, EpTm257, EpT258, EpTm258, EpT281 or EpTm281 cDNA of ATCC® Accession 207222, Accession number 207215, Accession Number 207217, Accession Number 207221, or patent deposit number PTA-224, wherein said nucleic acid molecules encode polypeptides or proteins that exhibit at least one structural and/or functional feature of a polypeptide of the invention.

The invention also features nucleic acid molecules which include a nucleotide sequence encoding a protein having an amino acid sequence that is at least 40%, 45%, 50%, 55%, 60%, 65%, 75%, 85%, 95%, or 98% identical to the amino acid sequence of SEQ ID NO:3, the amino acid sequence encoded by an EpT253 cDNA of ATCC® Accession Number 207222, or a complement thereof.

The invention also features nucleic acid molecules which include a nucleotide sequence encoding a protein having an amino acid sequence that is at least 95%, or 98%

identical to the amino acid sequence of SEQ ID NO:10, the amino acid sequence encoded by an EpTm253 cDNA of ATCC® Accession Number 207115, or a complement thereof.

The invention also features nucleic acid molecules which include a nucleotide sequence encoding a protein having an amino acid sequence that is at least 88%, 90%, 95% or 98% identical to the amino acid sequence of SEQ ID NO:17, the amino acid sequence encoded by an EpT257 cDNA of ATCC® Accession Number 207222, or a complement thereof.

The invention also features nucleic acid molecules which include a nucleotide sequence encoding a protein having an amino acid sequence that is at least 88%, 90%, 95%, or 98% identical to the amino acid sequence of SEQ ID NO:23, the amino acid sequence encoded by an EpTm257 cDNA of ATCC® Accession Number 207117, or a complement thereof.

The invention also features nucleic acid molecules which include a nucleotide sequence encoding a protein having an amino acid sequence that is at least 45%, 50%, 55%, 60%, 65%, 75%, 85%, 95%, or 98% identical to the amino acid sequence of SEQ ID NO:28, the amino acid sequence encoded by an EpT258 cDNA of ATCC® Accession Number 207222, or a complement thereof.

The invention also features nucleic acid molecules which include a nucleotide sequence encoding a protein having an amino acid sequence that is at least 45%, 50%, 55%, 60%, 65%, 75%, 85%, 95%, or 98% identical to the amino acid sequence of SEQ ID NO:39, the amino acid sequence encoded by an EpTm258 cDNA of ATCC® Accession Number 207221, or a complement thereof.

The invention also features nucleic acid molecules which include a nucleotide sequence encoding a protein having an amino acid sequence that is at least 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 75%, 85%, 95%, or 98% identical to the amino acid sequence of SEQ ID NO:48, the amino acid sequence encoded by an EpT281 cDNA of ATCC® Accession Number 207222, or a complement thereof.

The invention also features nucleic acid molecules which include a nucleotide sequence encoding a protein having an amino acid sequence that is at least 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 75%, 85%, 95%, or 98% identical to the amino acid sequence of SEQ ID NO:58, the amino acid sequence encoded by an EpTm281 of ATCC® patent deposit Number PTA-224, or a complement thereof.

The invention also features nucleic acid molecules which include a nucleotide sequence encoding a polypeptide or protein having an amino acid sequence that is at least 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 75%, 85%, 95%, or 98% identical to the amino acid sequence of SEQ ID NO:3, 10, 17, 23, 28, 39, 48, or 58, the amino acid

sequence encoded by EpT253, EpTm253, EpT257, EpTm257, EpT258, EpTm258, EpT281, or EpTm281 of ATCC® Accession Number 207222, Accession Number 207215, Accession Number 207217, or Accession Number 207221, patent deposit Number PTA-224, or a complement thereof, wherein the polypeptide or protein encoded by the nucleotide sequence also exhibits at least one structural and/or functional feature of a polypeptide of the invention.

In preferred embodiments, the nucleic acid molecules have the nucleotide sequence of SEQ ID NO:1, 2, 8, 9, 15, 16, 21, 22, 26, 27, 37, 38, 46, 47, 56 or 57, or the nucleotide sequence of the cDNA clones of ATCC® Accession Number 207222, 207215, 207217, 207221, 207222, or PTA-224.

Also within the invention are nucleic acid molecules which encode a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:3, or a fragment including at least 10, 15, 20, 25, 30, 50, 75, 100, 125, 150, 175, 200, 225, 230 or 240 contiguous amino acids of SEQ ID NO:3, or the amino acid sequence encoded by an EpT253 cDNA of ATCC® Accession Number 207222.

Also within the invention are nucleic acid molecules which encode a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:17, or a fragment including at least 10, 15, 20, 25, 30, 50, 75, 100, 125, 150, 175, 200, 225, 230 or 240 contiguous amino acids of SEQ ID NO:10, or the amino acid sequence encoded by an EpTm253 cDNA of ATCC® Accession Number 207215.

Also within the invention are nucleic acid molecules which encode a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:10, or a fragment including at least 360, 370, 380, 390 or 400 contiguous amino acids of SEQ ID NO:17, or the amino acid sequence encoded by an EpT257 cDNA of ATCC® Accession Number 207222.

Also within the invention are nucleic acid molecules which encode a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:23, or a fragment including at least 360, 370, 380, 390 or 400 contiguous amino acids of SEQ ID NO:23, or the amino acid sequence encoded by an EpTm257 cDNA of ATCC® Accession Number 207217.

Also within the invention are nucleic acid molecules which encode a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:3, or a fragment including at least 15, 25, 30, 50, 75, 100, 125, 150, 175, 200, 225, 250, 275, 300, 350 or 360 contiguous amino acids of SEQ ID NO:28, or the amino acid sequence encoded by an EpT258 cDNA of ATCC® Accession Number 207222.

Also within the invention are nucleic acid molecules which encode a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:39, or a fragment including at least 160, 175, 200, 225, 250, 275, 300, 350, 375 or 385 contiguous amino acids of SEQ

ID NO:39, or the amino acid sequence encoded by an EpT258 cDNA of ATCC® Accession Number 207221.

Also within the invention are nucleic acid molecules which encode a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:48, or a fragment including at least 15, 25, 30, 50, 75, 100, 125, 150, 175, 200, 225, 235 or 240 contiguous amino acids of SEQ ID NO:48, or the amino acid sequence encoded by an EpT281 cDNA of ATCC® Accession Number 207222.

Also within the invention are nucleic acid molecules which encode a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:58, or a fragment including at least 15, 25, 30, 50, 75, 100, 125, 150, 175 or 200 contiguous amino acids of SEQ ID NO:58, or the amino acid sequence encoded by an EpTm281 cDNA of ATCC® patent deposit Number PTA-224.

The invention also features nucleic acid molecules which encode a polypeptide fragment of at least 15, 25, 30, 50, 75, 100, 125, 150, 175, 200 or more contiguous amino acids of SEQ ID NO:3, 10, 17, 23, 28, 39, 48 or 58, or the amino acid sequence encoded by EpT253, EpTm253, EpT257, EpTm257, EpT258, EpTm258, EpT281 or EpTm281 of ATCC® Accession Number 207222, Accession Number 207215, Accession Number 207217, Accession Number 207221 or patent deposit Number PTA-224, wherein the fragment also exhibits at least one structural and/or functional feature of a polypeptide of the invention.

The invention includes nucleic acid molecules which encode a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:3, 10, 17, 23, 28, 39, 48, 58, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162 or 164, or the amino acid sequence encoded by a cDNA of ATCC® Accession Number 207222, Accession Number 207215, Accession Number 207217, Accession Number 207221 or patent deposit Number PTA-224, wherein the nucleic acid molecule hybridizes to a nucleic acid molecule consisting of a nucleic acid sequence encoding SEQ ID NO:3, 10, 28, 39, 48, 58, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162 or 164, or the amino acid sequence encoded by a cDNA of ATCC® Accession Number 207222, Accession Number 207215, Accession Number 207217, Accession Number 207221 or patent deposit Number PTA-224, or a complement thereof under stringent conditions.

Also within the invention are isolated polypeptides or proteins having an amino acid sequence that is at least about 40%, preferably 45%, 55%, 65%, 75%, 85%, 95% or

98% identical to the amino acid sequence of SEQ ID NO:3, or the amino acid sequence encoded by an EpT253 cDNA of ATCC® Accession Number 207222.

Also within the invention are isolated polypeptides or proteins having an amino acid sequence that is at least about 40%, preferably 45%, 50%, 55%, 65%, 75%, 85%, 95% or 98% identical to the amino acid sequence of SEQ ID NO:10, or the amino acid sequence encoded by an EpTm253 cDNA of ATCC® Accession Number 207215.

Also within the invention are isolated polypeptides or proteins having an amino acid sequence that is at least 88%, 90%, 95% or 98% identical to the amino acid sequence of SEQ ID NO:17, or the amino acid sequence encoded by an EpT257 cDNA of ATCC® Accession Number 207222.

Also within the invention are isolated polypeptides or proteins having an amino acid sequence that is at least 88%; 90%, 95% or 98% identical to the amino acid sequence of SEQ ID NO:23, or the amino acid sequence encoded by an EpTm257 cDNA of ATCC® Accession Number 207217.

Also within the invention are isolated polypeptides or proteins having an amino acid sequence that is at least about 30%, preferably 35%, 45%, 55%, 65%, 75%, 85%, 95% or 98% identical to the amino acid sequence of SEQ ID NO:28, or the amino acid sequence encoded by an EpT258 cDNA of ATCC® Accession Number 207222.

Also within the invention are isolated polypeptides or proteins having an amino acid sequence that is at least about 30%, preferably 35%, 40%, 45%, 50%, 55%, 65%, 75%, 85%, 95% or 98% identical to the amino acid sequence of SEQ ID NO:39, or the amino acid sequence encoded by an EpTm258 cDNA of ATCC® Accession Number 207221.

Also within the invention are isolated polypeptides or proteins having an amino acid sequence that is at least about 30%, preferably 35%, 45%, 55%, 65%, 75%, 85%, 95% or 98% identical to the amino acid sequence of SEQ ID NO:48, or the amino acid sequence encoded by an EpT281 cDNA of ATCC® Accession Number 207222.

Also within the invention are isolated polypeptides or proteins having an amino acid sequence that is at least about 30%, preferably 35%, 40%, 45%, 50%, 55%, 65%, 75%, 85%, 95% or 98% identical to the amino acid sequence of SEQ ID NO:58, or the amino acid sequence encoded by an EpTm281 cDNA of ATCC® patent deposit Number PTA-224.

The invention also features isolated polypeptides or proteins having an amino acid sequence that is at least about 30%, preferably 35%, 40%, 45%, 50%, 55%, 65%, 75%, 85%, 95% or 98% identical to the amino acid sequence of SEQ ID NO:3, 10, 17, 23, 28, 39, 48 or 58, or the amino acid sequence encoded by EpT253, EpTm253, EpT257,

EpTm257, EpT258, EpTm258, EpT281 or EpTm281 of ATCC® Accession Number 207222, Accession Number 207215, Accession Number 207217, Accession Number 207221, patent deposit Number PTA-224, wherein the protein or polypeptides also exhibit at least one structural and/or functional feature of a polypeptide of the invention.

Also within the invention are isolated polypeptides or proteins which are encoded by a nucleic acid molecule having a nucleotide sequence that is at least about 30%, preferably 35%, 40%, 45%, 50%, 55%, 60%, 65%, 75%, 85%, 95% or 98% identical to the nucleic acid sequence encoding SEQ ID NO:3, and isolated polypeptides or proteins which are encoded by a nucleic acid molecule having a nucleotide sequence which hybridizes under stringent hybridization conditions to a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:1 or SEQ ID NO:2, a complement thereof, or the non-coding strand of an EpT253 cDNA of ATCC® Accession Number 207222.

Also within the invention are isolated polypeptides or proteins which are encoded by a nucleic acid molecule having a nucleotide sequence that is at least about 30%, preferably 35%, 40%, 45%, 50%, 55%, 60%, 65%, 75%, 85%, 95% or 98% identical to the nucleic acid sequence encoding SEQ ID NO:10, and isolated polypeptides or proteins which are encoded by a nucleic acid molecule having a nucleotide sequence which hybridizes under stringent hybridization conditions to a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:8 or SEQ ID NO:9, a complement thereof, or the non-coding strand of an EpTm253 cDNA of ATCC® Accession Number 207215.

Also within the invention are isolated polypeptides or proteins which are encoded by a nucleic acid molecule having a nucleotide sequence that is at least about 45%, 50%, 55%, 60%, 65%, 75%, 85%, 95% or 98% identical to the nucleic acid sequence encoding SEQ ID NO:28, and isolated polypeptides or proteins which are encoded by a nucleic acid molecule having a nucleotide sequence which hybridizes under stringent hybridization conditions to a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:26 or SEQ ID NO:27, a complement thereof, or the non-coding strand of an EpT258 cDNA of ATCC® Accession Number 207222.

Also within the invention are isolated polypeptides or proteins which are encoded by a nucleic acid molecule having a nucleotide sequence that is at least about 45%, 50%, 55%, 60%, 65%, 75%, 85%, 95% or 98% identical to the nucleic acid sequence encoding SEQ ID NO:39, and isolated polypeptides or proteins which are encoded by a nucleic acid molecule having a nucleotide sequence which hybridizes under stringent hybridization conditions to a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:37 or SEQ ID NO:38, a complement thereof, or the non-coding strand of an EpTm258 cDNA of ATCC® Accession Number 207221.

Also within the invention are isolated polypeptides or proteins which are encoded by a nucleic acid molecule having a nucleotide sequence that is at least about 30%, preferably 35%, 40%, 45%, 50%, 55%, 60%, 65%, 75%, 85%, 95% or 98% identical to the nucleic acid sequence encoding SEQ ID NO:48, and isolated polypeptides or proteins which are encoded by a nucleic acid molecule having a nucleotide sequence which hybridizes under stringent hybridization conditions to a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:46 or SEQ ID NO:47, a complement thereof, or the non-coding strand of an EpT281 cDNA of ATCC® Accession Number 207222.

Also within the invention are isolated polypeptides or proteins which are encoded by a nucleic acid molecule having a nucleotide sequence that is at least about 30%, preferably 35%, 40%, 45%, 50%, 55%, 60%, 65%, 75%, 85%, 95% or 98% identical to the nucleic acid sequence encoding SEQ ID NO:58, and isolated polypeptides or proteins which are encoded by a nucleic acid molecule having a nucleotide sequence which hybridizes under stringent hybridization conditions to a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:56 or SEQ ID NO:57, a complement thereof, or the non-coding strand of an EpTm281 cDNA of ATCC® patent deposit Number PTA-224.

The invention also features isolated polypeptides or proteins which are encoded by a nucleic acid molecule having a nucleotide sequence that is at least about 30%, preferably 35%, 40%, 45%, 50%, 55%, 60%, 65%, 75%, 85%, 95% or 98% identical to a nucleic acid sequence encoding SEQ ID NO:3, 10, 17, 23, 28, 39, 48, 58, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162 or 164, isolated polypeptides or proteins which are encoded by a nucleic acid molecule having a nucleotide sequence which hybridizes under stringent hybridization conditions to a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:1, 2, 8, 9, 15, 16, 21, 22, 26, 27, 37, 38, 46, 47, 56, 57, 77, 101, 103, 104, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191 or 192, a complement thereof, or the non-coding strand of EpT253, EpTm253, EpT257, EpTm257, EpT258, EpTm258, EpT281, EpTm281 of ATCC® Accession Number 207222, Accession Number 207215, Accession Number 207217, Accession Number 207221, patent deposit Number PTA-224, wherein polypeptides or proteins also exhibit at least one structural and/or functional feature of a polypeptide of the invention.

Also within the invention are polypeptides which are naturally occurring allelic variants of a polypeptide that includes the amino acid sequence of SEQ ID NO:3, 10, 17,

23, 28, 39, 48 or 58, or the amino acid sequence encoded by a cDNA of ATCC® Accession Number 207222, Accession Number 207215, Accession Number 207217 Accession Number 207221, or patent deposit Number PTA-224, wherein the polypeptide is encoded by a nucleic acid molecule which hybridizes to a nucleic acid molecule having the sequence of SEQ ID NO:1, 2, 8, 9, 15, 16, 21, 22, 26, 27, 37, 38, 46, 47, 56 or 57, or a complement thereof under stringent conditions.

The invention also features nucleic acid molecules that hybridize under stringent conditions to a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:1 or 2, or an EpT253 cDNA of ATCC® Accession Number 207222, or a complement thereof. In other embodiments, the nucleic acid molecules are at least 450, 500, 550, 600, 650, 700, 750, 800, 1000, 1100, 1200 or 1300 contiguous nucleotides in length and hybridize under stringent conditions to a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1 or 2, an EpT253 cDNA of ATCC® Accession Number 207222, or a complement thereof.

The invention also features nucleic acid molecules that hybridize under stringent conditions to a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:8 or SEQ ID NO:9, an EpTm253 cDNA of ATCC® Accession Number 207215, or a complement thereof. In other embodiments, the nucleic acid molecules are at least 540, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1050, 1100, 1159, 1200, or 1250 contiguous nucleotides in length and hybridize under stringent conditions to a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:8 or SEQ ID NO:9, an EpTm253 cDNA of ATCC® Accession Number 207215, or a complement thereof.

The invention also features nucleic acid molecules that hybridize under stringent conditions to a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:15 or SEQ ID NO:16, an EpT257 cDNA of ATCC® Accession Number 207222, or a complement thereof and encode a polypeptide comprising the amino acid sequence of SEQ ID NO:17, or encode a polypeptide comprising at least 360, 370, 380, 390 or 400 contiguous amino acids or SEQ ID NO:17.

The invention also features nucleic acid molecules that hybridize under stringent conditions to a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:21 or SEQ ID NO:22, an EpTm257 cDNA of ATCC® Accession Number 207217, or a complement thereof, and encode a polypeptide comprising the amino acid sequence of SEQ ID NO:23, or a polypeptide comprising at least 360, 370, 380, 390, or 400 contiguous amino acids of SEQ ID NO:23.

The invention also features nucleic acid molecules that hybridize under stringent conditions to a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:26 or

SEQ ID NO:27, an EpT258 cDNA of ATCC® Accession Number 207222, or a complement thereof. In other embodiments, the nucleic acid molecules are at least 550, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700 or 1800 contiguous nucleotides in length and hybridize under stringent conditions to a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:26 or SEQ ID NO:27, an EpT258 cDNA of ATCC® Accession Number 207222, or a complement thereof.

The invention also features nucleic acid molecules that hybridize under stringent conditions to a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:37 or SEQ ID NO:38, an EpTm258 cDNA of ATCC® Accession Number 207221, or a complement thereof. In other embodiments, the nucleic acid molecules are at least 650, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700 or 1800 contiguous nucleotides in length and hybridize under stringent conditions to a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:37 or SEQ ID NO:38, an EpTm258 cDNA of ATCC® Accession Number 207221, or a complement thereof.

The invention also features nucleic acid molecules that hybridize under stringent conditions to a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:46 or 47, an EpTm281 cDNA of ATCC® Accession Number 207222, or a complement thereof. In other embodiments, the nucleic acid molecules are at least 710, 750, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700 or 1800 contiguous nucleotides in length and hybridize under stringent conditions to a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:46 or SEQ ID NO:47, an EpT281 cDNA of ATCC® Accession Number 207222, or a complement thereof.

The invention also features nucleic acid molecules that hybridize under stringent conditions to a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:56 or 57, an EpTm281 cDNA of ATCC® patent deposit Number PTA-224, or a complement thereof. In other embodiments, the nucleic acid molecules are at least 580, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800 or 1850 contiguous nucleotides in length and hybridize under stringent conditions to a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:56 or SEQ ID NO:57, an EpTm281 cDNA of ATCC® patent deposit Number PTA-224, or a complement thereof.

The invention also features nucleic acid molecules that hybridize under stringent conditions to a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:1, 2, 8, 9, 15, 16, 21, 22, 26, 27, 37, 38, 46, 47, 56, 57, 77, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191 or 192, or a

nucleotide sequence of EpT253, EpTm253, EpT257, EpTm257, EpT258, EpTm258, EpT281 or EpTm281 of ATCC® Accession Number 207222, Accession Number 207215, Accession Number 207217, Accession Number 207221, patent deposit Number PTA-224, or complement thereof, wherein such nucleic acid molecules encode polypeptides or proteins that exhibit at least one structural and/or functional feature of a polypeptide of the invention.

The invention also features nucleic acid molecules at least 15, preferably at least 50, at least 75, at least 100, at least 150, at least 200, at least 250, at least 300, at least 350, at least 400, at least 500, at least 600, at least 700, at least 800, at least 1000, at least 1100 or at least 1200 or more contiguous nucleotides in length which hybridize under stringent conditions to a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1, 2, 8, 9, 15, 16, 21, 22, 26, 27, 37, 38, 46, 47, 56, 57, 77, 80, 91, 100, 101, 103, 104, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191 or 192, or a nucleotide sequence of EpT253, EpTm253, EpT257, EpTm257, EpT258, EpTm258, EpT281 or EpTm281 of ATCC® Accession Number 207222, Accession Number 207215, Accession Number 207217, Accession Number 207221, patent deposit Number PTA-224, or a complement thereof, wherein said nucleic acid molecules encode polypeptides or proteins that exhibit at least one structural and/or functional feature of a polypeptide of the invention.

In one embodiment, the invention provides an isolated nucleic acid molecule which is antisense to the coding strand of a nucleic acid of the invention.

Another aspect of the invention provides vectors, *e.g.*, recombinant expression vectors, comprising a nucleic acid molecule of the invention. In another embodiment, the invention provides host cells containing such a vector or engineered to contain and/or express a nucleic acid molecule of the invention. The invention also provides methods for producing a polypeptide of the invention by culturing, in a suitable medium, a host cell of the invention such that a polypeptide of the invention is produced.

Another aspect of this invention features isolated or recombinant proteins and polypeptides of the invention. Preferred proteins and polypeptides possess at least one biological activity possessed by the corresponding naturally-occurring human polypeptide. An activity, a biological activity, or a functional activity of a polypeptide or nucleic acid of the invention refers to an activity exerted by a protein, polypeptide or nucleic acid molecule of the invention on a responsive cell as determined *in vivo* or *in vitro*, according to standard techniques. Such activities can be a direct activity, such as an association with

or an enzymatic activity on a second protein, or an indirect activity, such as a cellular signaling activity mediated by interaction of the protein with a second protein.

For TANGO 253, biological activities include, *e.g.*, (1) the ability to modulate (this term, as used herein, includes, but is not limited to, "stabilize", promote, inhibit or disrupt, protein-protein interactions (*e.g.*, homophilic and/or heterophilic), and protein-ligand interactions, *e.g.*, in receptor-ligand recognition; (2) the ability to modulate the development, differentiation, maturation, proliferation and/or activity of cells of the central nervous system such as neurons, glial cells (*e.g.*, astrocytes and oligodendrocytes), and Schwann cells; (3) the ability to modulate the development of central nervous system; (4) the ability to modulate the development, differentiation, maturation, proliferation and/or activity of renal cells; (5) the ability to modulate the development, differentiation, maturation, proliferation and/or activity of testical cells, such as germ cells, leydig cells and Sertoli cells; (6) the ability to modulate the development, differentiation, maturation, proliferation and/or activity of ovarian cells; (7) ability to modulate cell-cell interactions and/or cell-extracellular matrix interactions; (8) the ability to modulate the host immune response, *e.g.*, by modulating one or more elements in the serum complement cascade; (9) the ability to modulate the proliferation, differentiation and/or activity of cells that form blood vessels and coronary tissue (*e.g.*, coronary smooth muscle cells and/or blood vessel endothelial cells); (10) the ability to modulate intracellular signaling cascades (*e.g.*, signal transduction cascades); and (11) the ability to modulate adipocyte function.

For TANGO 257, biological activities include, *e.g.*, (1) the ability to modulate the development, differentiation, proliferation and/or activity of neuronal cells, *e.g.*, olfactory neurons (2) the ability to modulate the development, differentiation, proliferation and/or activity of pulmonary system cells, *e,g.*, lung cell types; (4) the ability to modulate the development, differentiation, maturation, proliferation and/or activity of bone cells such as osteocytes, osteoblasts and osteoclasts (*e.g.*, the ability promote the development of osteocytes); (5) the ability to modulate the development of bone structures such as the skull, the basisphenoid bone, the upper and lower incisor teeth, the vertebral column, the sternum, the scapula, and the femur during embryogenesis; (6) the ability to modulate the development, differentiation, maturation, proliferation and/or activity of renal cells; (7) the ability to modulate the development, differentiation, maturation, proliferation and/or activity of intestinal cells such as M cells; (8) the ability to modulate cell-cell interactions and/or cell-extracellular matrix interactions, *e.g.*, neuronal cell-extracellular matrix interactions; (9) the ability to modulate cell proliferation, *e.g.*, abnormal cell proliferation; and (10) the ability to modulate the development, differentiation, proliferation and/or

activity of cells that form blood vessels and coronary tissue, *e.g.*, coronary smooth muscle cells and/or blood vessel endothelial cells.

For INTERCEPT 258, biological activities include, *e.g.*, (1) the ability to modulate protein-protein interactions (*e.g.*, homophilic and/or heterophilic), and protein-ligand interactions, *e.g.*, in receptor-ligand recognition; (2) the ability to modulate cell-cell interactions; (3) the ability to modulate the host immune response; (4) the ability to modulate the development, differentiation, maturation, proliferation and/or activity of pulmonary system cells such as bronchial cells; (5) the ability to modulate the development, differentiation, maturation, proliferation and/or activity of renal cells; (5) the ability to modulate the development, differentiation, maturation, proliferation and/or activity of cardiac cells such cardiac myocytes; (6) the ability to modulate the development of brown fat (*e.g.*, the promotion of the development of brown fat); (7) the ability to modulate the development, differentiation, maturation, proliferation and/or activity of endothelial cells; (8) the ability to modulate cell proliferation, *e.g.*, gastrointestinal tract epithelial cell proliferation; (9) the ability to modulate intracellular signaling cascades (*e.g.*, signal transduction cascades); and (10) the ability to modulate thrombosis (*e.g.*, the ability to facilitate the removal of blood clots) and/or vascularization (*e.g.*, the promotion of vascularization).

For TANGO 281, biological activities include, *e.g.*, (1) the ability to modulate, *e.g.*, stabilize, promote, inhibit or disrupt protein-protein interactions (*e.g.*, homophilic and/or heterophilic), and protein-ligand interactions, *e.g.*, in receptor-ligand recognition; (2) the ability to modulate cell-cell interactions; (3) the ability to modulate the host immune response; (4) the ability to modulate the proliferation, differentiation and/or activity of hematopoeitic cells (*e.g.* megakaryocytes); (5) the ability to modulate the development, differentiation, maturation, proliferation and/or activity of pulmonary system cells; (6) the ability to modulate the development, differentiation, maturation, proliferation and/or activity intestinal cells such as M cells; (7) the ability to modulate the development, differentiation, maturation, proliferation and/or activity of stomach cells such as cells of the gastric epithelium; (8) the ability to modulate intracellular signaling cascades (*e.g.*, signal transduction cascades); and (9) the ability to modulate platelet function (*e.g.*, the promotion of platelet aggregation).

In one embodiment, a polypeptide of the invention has an amino acid sequence sufficiently identical to an identified domain of a polypeptide of the invention. As used herein, the term "sufficiently identical" refers to a first amino acid or nucleotide sequence which contains a sufficient or minimum number of identical or equivalent (*e.g.*, with a similar side chain) amino acid residues or nucleotides to a second amino acid or nucleotide

sequence such that the first and second amino acid or nucleotide sequences have or encode a common structural domain and/or common functional activity. For example, amino acid or nucleotide sequences which contain or encode a common structural domain having about 60% identity, preferably 65% identity, more preferably 75%, 85%, 95%, 98% or more identity are defined herein as sufficiently identical.

In one embodiment, a TANGO 253 protein includes at least one or more of the following domains: a signal sequence, a collagen domain and a C1q domain.

In one embodiment, a TANGO 257 protein includes at least a signal peptide.

In one embodiment, an INTERCEPT 258 includes at least one or more of the following domains: a signal sequence, an extracellular domain, an immunoglobulin (Ig) domain, a transmembrane domain, and an intracellular or cytoplasmic domain.

In one embodiment, a TANGO 281 protein includes at least one or more of the following domains: a signal sequence, an extracellular domain, a photosystem II 10 kD phosphoprotein domain, a transmembrane domain, and an intracellular or cytoplasmic domain.

The polypeptides of the present invention, or biologically active portions thereof, can be operably linked to a heterologous amino acid sequence to form fusion proteins. The invention further features antibodies, such as monoclonal or polyclonal antibodies, that specifically bind a polypeptide of the invention. In addition, the polypeptides of the invention or biologically active portions thereof can be incorporated into pharmaceutical compositions, which optionally include pharmaceutically acceptable carriers.

In another aspect, the present invention provides methods for detecting the presence, activity or expression of a polypeptide of the invention in a biological sample by contacting the biological sample with an agent capable of detecting an indicator of the presence, activity or expression such that the presence activity or expression of a polypeptide of the invention is detected in the biological sample.

In another aspect, the invention provides methods for modulating activity of a polypeptide of the invention comprising contacting a cell with an agent that modulates (inhibits or stimulates) the activity or expression of a polypeptide of the invention such that activity or expression in the cell is modulated. In one embodiment, the agent is an antibody that specifically binds to a polypeptide of the invention.

In another embodiment, the agent modulates expression of a polypeptide of the invention by modulating transcription, splicing, or translation of an mRNA encoding a polypeptide of the invention. In yet another embodiment, the agent is a nucleic acid molecule having a nucleotide sequence that is antisense to the coding strand of an mRNA encoding a polypeptide of the invention.

The present invention also provides methods to treat a subject having a disorder characterized by aberrant activity of a polypeptide of the invention or aberrant expression of a nucleic acid of the invention by administering an agent which is a modulator of the activity of a polypeptide of the invention or a modulator of the expression of a nucleic acid of the invention to the subject. In one embodiment, the modulator is a protein of the invention. In another embodiment, the modulator is a nucleic acid of the invention. In other embodiments, the modulator is a peptide, peptidomimetic, or other small molecule.

The present invention also provides diagnostic assays for identifying the presence or absence of a genetic lesion or mutation characterized by at least one of: (i) aberrant modification or mutation of a gene encoding a polypeptide of the invention; (ii) mis-regulation of a gene encoding a polypeptide of the invention; and (iii) aberrant post-translational modification of the invention wherein a wild-type form of the gene encodes a protein having the activity of the polypeptide of the invention.

In another aspect, the invention provides a method for identifying a compound that binds to or modulates the activity of a polypeptide of the invention. In general, such methods entail measuring a biological activity of the polypeptide in the presence and absence of a test compound and identifying those compounds which alter the activity of the polypeptide.

The invention also features methods for identifying a compound which modulates the expression of a polypeptide or nucleic acid of the invention by measuring the expression of the polypeptide or nucleic acid in the presence and absence of the compound.

In another aspect, the invention provides substantially purified antibodies or fragments thereof, including human, humanized, chimeric and non-human antibodies or fragments thereof, which antibodies or fragments specifically bind to a polypeptide comprising an amino acid sequence of SEQ ID NO: 3, 10, 17, 23, 28, 39, 48, 58, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162 or 164, or the amino acid sequence encoded by the EpT253, EpTm253, EpT257, EpTm257, EpT258, EpTm258, EpT281 or EpTm281 cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207222, Accession Number 207215, Accession number 207217, Accession number 207221, or patent deposit Number PTA-224.

In another aspect, the invention provides substantially purified antibodies or fragments thereof, including, *e.g.*, human, non-human, chimeric and humanized antibodies, which antibodies or fragments thereof specifically bind to a polypeptide comprising at least 15 contiguous amino acids of the amino acid sequence of SEQ ID NO:

3, 10, 17, 23, 28, 39, 48, 58, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162 or 164, or the amino acid sequence encoded by the EpT253, EpTm253, EpT257, EpTm257, EpT258, EpTm258, EpT281 or EpTm281 cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207222, Accession number 207215, Accession number 207217, Accession number 207221, or patent deposit number PTA-224, or a complement thereof.

In another aspect, the invention provides substantially purified antibodies or fragments thereof, including, *e.g.*, human, non-human, chimeric and humanized antibodies, which antibodies or fragments thereof specifically bind to a polypeptide comprising at least 95% identical to the amino acid sequence of SEQ ID NO: 3, 10, 17, 23, 28, 39, 48, 58, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162 or 164, or the amino acid sequence encoded by the EpT253, EpTm253, EpT257, EpTm257, EpT258, EpTm258, EpT281 or EpTm281 cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207222, Accession number 207215, Accession number 207217, Accession number 207221, or patent deposit number PTA-224, or a complement thereof.

In another aspect, the invention provides substantially purified antibodies or fragments thereof, including, *e.g.*, human, non-human, chimeric and humanized antibodies, which antibodies or fragments thereof specifically bind to a polypeptide encoded by a nucleic acid molecule which hybridizes to the nucleic acid molecule of SEQ ID NO:1, 2, 8, 9, 15, 16, 21, 22, 26, 27, 37, 38, 46, 47, 56, 57, 77, 80, 91, 100, 101, 103, 104, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191 or 192 under conditions of hybridization of 6 X SSC at 45°C and washing in 0.2 X SSC, 0.1% SDS at 65°C.

Any of the antibodies of the invention can be conjugated to a therapeutic moiety or to a detectable substance. Non-limiting examples of detectable substances that can be conjugated to the antibodies of the invention are an enzyme, a prosthetic group, a fluorescent material, a luminescent material, a bioluminescent material, and a radioactive material.

The invention also provides a kit containing an antibody of the invention conjugated to a detectable substance, and instructions for use. Still another aspect of the invention is a pharmaceutical composition comprising an antibody of the invention and a pharmaceutically acceptable carrier. In preferred embodiments, the pharmaceutical

composition contains an antibody of the invention, a therapeutic moiety, and a pharmaceutically acceptable carrier.

Other features and advantages of the invention will be apparent from the following detailed description and claims.

Brief Description of the Drawings

FIGURES 1A-AB depict the cDNA sequence of human TANGO 253 (SEQ ID NO:1) and the predicted amino acid sequence of human TANGO 253 (SEQ ID NO:3). The open reading frame of SEQ ID NO:1 extends from nucleotide 188 to nucleotide 916 of SEQ ID NO:1 (SEQ ID NO:2).

FIGURE 2 depicts a hydropathy plot of human TANGO 253. Relatively hydrophobic regions of the protein are above the dashed horizontal line, and relatively hydrophilic regions of the protein are below the dashed horizontal line. The cysteine residues (cys) are indicated by short vertical lines just below the hydropathy trace. The dashed vertical line separates the signal sequence (amino acids 1 to 15 of SEQ ID NO:3; SEQ ID NO:5) on the left from the mature protein (amino acids 16 to 243 of SEQ ID NO:3; SEQ ID NO:4) on the right. Below the hydropathy plot, the amino acid sequence of human TANGO 253 is depicted.

FIGURES 3A-3B depict a cDNA sequence of mouse TANGO 253 (SEQ ID NO:8) and the predicted amino acid sequences of mouse TANGO 253 (SEQ ID NO:10). The open reading frame of SEQ ID NO:10 extends from nucleotide 135 to 863 of SEQ ID NO:10 (SEQ ID NO:9).

FIGURE 4 depicts a hydropathy plot of mouse TANGO 253. Relatively hydrophobic regions of the protein are shown above the dashed horizontal line, and relatively hydrophilic regions of the protein are below the dashed horizontal line. The cysteine residues (cys) are indicated by short vertical lines just below the hydropathy trace. The dashed vertical line separates the signal sequence (amino acids 1 to 15 of SEQ ID NO:10; SEQ ID NO:12) on the left from the mature protein (amino acids 16 to 243 of SEQ ID NO:10; SEQ ID NO:11) on the right. Below the hydropathy plot, the amino acid sequence of mouse TANGO 253 is depicted.

FIGURE 5 depicts an alignment of the amino acid sequence of human TANGO 253 (SEQ ID NO:3) and the amino acid sequence of mouse TANGO 253 (SEQ ID NO:10). The alignment demonstrates that the amino acid sequences of human and mouse TANGO 253 are 93.8% identical. This alignment was performed using the ALIGN program with a PAM120 scoring matrix, a gap length penalty of 12 and a gap penalty of 4.

FIGURES 6A-6B depict alignments of the amino acid sequence of human adipocyte complement-mediated protein precursor (SEQ ID NO:20; Swiss Prot Accession Number Q15848) and the amino acid sequence of human TANGO 253 (SEQ ID NO:3; 6A) or mouse TANGO 253 (SEQ ID NO:10; 6B). 6A shows the amino acid sequences of human adipocyte complement-mediated protein precursor and human TANGO 253 are 38.7% identical. 6B shows the amino acid sequences of human adipocyte complement-mediated precursor procursor protein and mouse TANGO 253 are 38.3% identical. These alignments were performed using the ALIGN alignment program with a PAM120 scoring matrix, a gap length penalty of 12, and a gap penalty of 4.

FIGURES 7A-7C depict alignments of the nucleotide sequence of human adipocyte complement-mediated protein precursor (SEQ ID NO:32; GenBank Accession Number A1417523) and the nucleotide sequence of human TANGO 253 (SEQ ID NO:1). The nucleotide sequences of human adipocyte complement-mediated protein precursor and human TANGO 253 are 29.1% identical. These alignments were performed using the ALIGN alignment program with a PAM120 scoring matrix, a gap length penalty of 12, and a gap penalty of 4.

FIGURES 8A-8C depict alignments of the nucleotide sequence of human adipocyte complement-mediated protein precursor (SEQ ID NO:32; GenBank Accession Number A1417523) and the nucleotide sequence of mouse TANGO 253 (SEQ ID NO:8). The nucleotide sequences of human adipocyte complement-mediated protein precursor and mouse TANGO 253 are 30.4% identical. These alignments were performed using the ALIGN alignment program with a PAM120 scoring matrix, a gap length penalty of 12, and a gap penalty of 4.

FIGURES 9A-9B depict the cDNA sequence of human TANGO 257 (SEQ ID NO:15) and the predicted amino acid sequence of human TANGO 257 (SEQ ID NO:17). The open reading frame of SEQ ID NO:16 extends from nucleotide 88 to nucleotide 1305 of SEQ ID NO:15 (SEQ ID NO:16).

FIGURE 10 depicts a hydropathy plot of human TANGO 257. Relatively hydrophobic regions of the protein are shown above the dashed horizontal line, and relatively hydrophilic regions of the protein are below the dashed horizontal line. The cysteine residues (cys) and potential N-glycosylation sites (Ngly) are indicated by short vertical lines just below the hydropathy trace. The dashed vertical line separates the signal sequence (amino acids 1 to 21 of SEQ ID NO:16; SEQ ID NO:19) on the left from the mature protein (amino acids 22 to 406 of SEQ ID NO:16; SEQ ID NO:18) on the right. Below the hydropathy plot, the amino acid sequence of human TANGO 257 is depicted.

FIGURES 11A-11B depict a cDNA sequence of mouse TANGO 257 (SEQ ID NO:21) and the predicted amino acid sequence of mouse TANGO 257 (SEQ ID NO:23). The open reading frame of SEQ ID NO:21 extends from nucleotide 31 to 1248 of SEQ ID NO:21 (SEQ ID NO:22).

FIGURE 12 depicts a hydropathy plot of mouse TANGO 257. Relatively hydrophobic regions of the protein are shown above the dashed horizontal line, and relatively hydrophilic regions of the protein are below the dashed horizontal line. The cysteine residues (cys) and potential N-glycosylation sites (Ngly) are indicated by short vertical lines just below the hydropathy trace. The dashed vertical line separates the signal sequence (amino acids 1 to 21 of SEQ ID NO:23; SEQ ID NO:25) on the left from the mature protein (amino acids 22 to 406 of SEQ ID NO:23; SEQ ID NO:24) on the right. Below the hydropathy plot, the amino acid sequence of mouse TANGO 257 is depicted.

FIGURE 13 depicts an alignment of the amino acid sequence of human TANGO 257 (SEQ ID NO:17) and the amino acid sequence of mouse TANGO 257 (SEQ ID NO:23). This alignment demonstrates that the amino acid sequences of human and mouse TANGO 257 are 94.1% identical. This alignment was performed using the ALIGN program with a PAM120 scoring matrix, a gap length penalty of 12 and a gap penalty of 4.

FIGURE 14 depicts an alignment of the amino acid sequence (SEQ ID NO:43) encoded by a nucleotide sequence referred to in PCT publication WO 98/39446 as "gene 64", and the amino acid sequence of human TANGO 257 (SEQ ID NO:17). Gene 64 encodes a 353 amino acid residue protein that exhibits homology with the human extracellular molecule olfactomedin, which is though to be involved in maintenance, growth and/or differentiation of chemosensory cilia on the apical dendrites of olfactory neurons. The polypeptide encoded by gene 64 also exhibits homology to human TANGO 257, which contains 406 amino acids (*i.e.*, an additional 53 amino acids carboxy to residue 353). The amino acid sequences of amino acid residues 1-353 of the gene 64-encoded polypeptide and human TANGO 257 are identical. As such, the overall amino acid sequence identity between the full length polypeptide encoded by gene 64, and the full-length human TANGO 257 polypeptide is approximately 87%. This alignment was performed using the ALIGN alignment program with a PAM120 scoring matrix, a gap length penalty of 12, and a gap penalty of 4.

FIGURES15A-15D depict an alignment of the nucleotide sequence of gene 64 (SEQ ID NO:66; PCT Publication WO 98/39446) and the nucleotide sequence of human TANGO 257 (SEQ ID NO:15). The nucleotide sequences of gene 64 and human TANGO 257 are 93.5% identical. It is noted, however, that among the differences between the two sequences is a cytosine nucleotide at human TANGO 257 (SEQ ID

NO:15) position 1146 that results in a human TANGO 257 amino acid sequence (SEQ ID NO:17) of 406 amino acids as opposed to the gene 64 amino acid sequence of only 353 amino acids (SEQ ID NO:43). Alignment of the nucleotide sequence of the gene 64 open reading frame and that of human TANGO 257 (SEQ ID NO:16) show that the two nucleotide sequences are 87.2% identical. These alignments were performed using the ALIGN program with a PAM220 scoring matrix, a gap length penalty of 12 and a gap penalty of 4.

FIGURE 16 depicts an alignment of the acid sequence of the gene 64-encoded polypeptide (SEQ ID NO:43) and the amino acid sequence of mouse TANGO 257 (SEQ ID NO:23). The sequences exhibit an overall amino acid sequence identity of approximately 81.8%. This alignment was performed using an ALIGN program with a PAM120 scoring matrix, a gap length penalty of 12 and a gap penalty of 4.

FIGURE 17A-17C depicts an alignment of the nucleotide sequence of gene 64 (SEQ ID NO:66) and the nucleotide sequence of mouse TANGO 257 (SEQ ID NO:21). The two sequences are approximately 76.2% identical. Alignment of the nucleotide sequence of the gene 64 open reading frame and that of mouse TANGO 257 (SEQ ID NO:22) show that the two nucleotide sequences are 77.8% identical. These alignments were performed using the ALIGN program with a PAM220 scoring matrix, a gap length penalty of 12 and a gap penalty of 4.

FIGURES 18A-18B depict the cDNA sequence of human INTERCEPT 258 (SEQ ID NO:26) and the predicted amino acid sequence of INTERCEPT 258 (SEQ ID NO:28). The open reading frame of SEQ ID NO:26 extends from nucleotide 153 to nucleotide 1262 of SEQ ID NO:26 (SEQ ID NO:27).

FIGURE 19 depicts a hydropathy plot of human INTERCEPT 258. Relatively hydrophobic regions of the protein are above the dashed horizontal line, and relatively hydrophilic regions of the protein are below the dashed horizontal line. The cysteine residues (Cys) and potential N-glycosylation sites (Ngly) are indicated by short vertical lines just below the hydropathy trace. Below the hydropathy plot, the amino acid sequence of human INTERCEPT 258 is depicted.

FIGURES 20A-20B depict a cDNA sequence of mouse INTERCEPT 258 (SEQ ID NO:37) and the predicted amino acid sequence of mouse INTERCEPT 258 (SEQ ID NO:39). The open reading frame of SEQ ID NO:37 extends from nucleotide 107 TO 1288 of SEQ ID NO:60 (SEQ ID NO:38).

FIGURE 21 depicts a hydropathy plot of mouse INTERCEPT 258. Relatively hydrophobic regions of the protein are shown above the dashed horizontal line, and relatively hydrophilic regions of the protein are below the dashed horizontal line. The

cysteine residues (cys) and potential N-glycosylation sites (Ngly) are indicated by short vertical lines just below the hydropathy trace. The dashed vertical line separates the signal sequence (amino acids 1 to 29 of SEQ ID NO:39; SEQ ID NO:41) on the left from the mature protein (amino acids 30 to 394 of SEQ ID NO:39; SEQ ID NO:40) on the right. Below the hydropathy plot, the amino acid sequence of mouse INTERCEPT 258 is depicted.

FIGURE 22 depicts an alignment of the amino acid sequence of human INTERCEPT 258 (SEQ ID NO:28) and the amino acid sequence of mouse INTERCEPT 258 (SEQ ID NO:39). The alignment demonstrates that the amino acid sequences of human and mouse INTERCEPT 258 are 62.8% identical. This alignment was performed using the ALIGN program with a PAM120 scoring matrix, a gap length penalty of 12 and a gap penalty of 4.

FIGURE 23 depicts an alignment of the amino acid sequence of human A33 antigen (SEQ ID NO:67; Swiss Prot Accession Number Q99795) and the amino acid sequence of human INTERCEPT 258 (SEQ ID NO:28). The A33 antigen is a transmembrane glycoprotein and member of the Ig superfamily that may be a cancer cell marker. The amino acid sequences of A33 antigen and human INTERCEPT 258 are 23% identical. This alignment was performed using the ALIGN alignment program with a PAM120 scoring matrix, a gap length penalty of 12, and a gap penalty of 4.

FIGURES 24A-24D depict an alignment of the nucleotide sequence of human A33 antigen (SEQ ID NO:68; Gen Bank Accession Number U79725) and the nucleotide sequence of human INTERCEPT 258 (SEQ ID NO:26). These two nucleotide sequences are 40.6% identical. The nucleotide sequence of the open reading frame of human A33 antigen and that of human INTERCEPT 258 are 44% identical. These alignments were performed using the ALIGN alignment program with a PAM120 scoring matrix, a gap length penalty of 12, and a gap penalty of 4.

FIGURE 25 depicts an alignment of the amino acid sequence of human A33 antigen (SEQ ID NO:67; Swiss Prot Accession Number Q99795) and the amino acid sequence of mouse INTERCEPT 258 (SEQ ID NO:39). These two amino acid sequences have an overall amino acid identity of 23%. This alignment was performed using the ALIGN alignment program with a PAM120 scoring matrix, a gap length penalty of 12, and a gap penalty of 4.

FIGURES 26A-26D depict an alignment of the nucleotide sequence of human A33 antigen (SEQ ID NO:68; GenBank Accession Number U79725) and the nucleotide sequence of mouse INTERCEPT 258 (SEQ ID NO:37). These two nucleotide sequences are 40% identical. The nucleotide sequence of the open reading frame of human A33

antigen and that of mouse INTERCEPT 258 are 43.2% identical. These alignments were performed using the ALIGN alignment program with a PAM120 scoring matrix, a gap length penalty of 12, and a gap penalty of 4.

FIGURE 27A-27E depict an alignment of the nucleotide sequence of human PECAM-1, an integrin expressed on endothelial cells (SEQ ID NO:72) and the nucleotide sequence of human INTERCEPT 258 (SEQ ID NO:26). These two nucleotide sequences are 40.5% identical. This alignment was performed using ALIGN alignment program with a PAM120 scoring matrix, a gap length of 12, and a gap penalty of 4.

FIGURE 28A-28B depict the cDNA sequence of human TANGO 281 (SEQ ID NO:46) and the predicted amino acid sequence of human TANGO 281 (SEQ ID NO:48). The open reading frame of SEQ ID NO:66 extends from nucleotide 65 to nucleotide 799 of SEQ ID NO:46 (SEQ ID NO:47).

FIGURE 29 depicts a hydropathy plot of human TANGO 281. Relatively hydrophobic regions of the protein are above the dashed horizontal line, and relatively hydrophilic regions of the protein are below the dashed horizontal line. The cysteine residues (cys) are indicated by short vertical lines just below the hydropathy trace. The dashed vertical line separates the signal sequence (amino acids 1 to 38 of SEQ ID NO:48; SEQ ID NO:49) on the left from the mature protein (amino acids 39 to 245 of SEQ ID NO:48; SEQ ID NO:50) on the right. Below the hydropathy plot, the amino acid sequence of human TANGO 281 is depicted.

FIGURE 30 depicts an alignment of the amino acid sequence of photosystem II 10 kD phosphoprotein domain (SEQ ID NO:69; GenBank Accession Number PF00737) and the amino acid sequence 97 to 146 of human TANGO 281 (SEQ ID NO:48). This alignment was performed using the ALIGN alignment program with a PAM120 scoring matrix, a gap length penalty of 12, and a gap penalty of 4.

FIGURES 31A-31B depict the cDNA sequence of mouse TANGO 281 (SEQ ID NO:56) and the predicted amino acid sequence of mouse TANGO 281 (SEQ ID NO:58). The open reading frame of SEQ ID NO:56 extends from nucleotide 90 to nucleotide 728 of SEQ ID NO:56 (SEQ ID NO:57).

Figure 32 depicts a hydropathy plot of mouse TANGO 281. Relatively hydrophobic regions of the protein are above the dashed horizontal line, and relatively hydrophilic regions of the protein are below the dashed horizontal line. The cysteine residues (cys) are indicated by short vertical lines just below the hydropathy trace. The dashed vertical line separates the signal sequence (amino acids 1 to 26 of SEQ ID NO:58; SEQ ID NO:59) on the left from the mature protein (amino acids 27 to 213 of SEQ ID

NO:58; SEQ ID NO:60) on the right. Below the hydropathy plot, the amino acid sequence of mouse TANGO 281 is depicted.

FIGURE 33 depicts an alignment of the amino acid sequence of human TANGO 281 (SEQ ID NO:48) and the amino acid sequence of mouse TANGO 281 (SEQ ID NO:58). The alignment demonstrates that the amino acid sequences of human and mouse TANGO 281 are 66.5% identical. This alignment was performed using the ALIGN program with a PAM120 scoring matrix, a gap length penalty of 12 and a gap penalty of 4.

Detailed Description of the Invention

The TANGO 253, TANGO 257, INTERCEPT 258 and TANGO 281 proteins and nucleic acid molecules comprise families of molecules having certain conserved structural and functional features. As used herein, the terms "family" or "families" are intended to mean two or more proteins or nucleic acid molecules having a common structural domain and having sufficient amino acid or nucleotide sequence identity as defined herein. Family members can be from either the same or different species. For example, a family can comprises two or more proteins of human origin, or can comprise one or more proteins of human origin and one or more of non-human origin. Members of the same family may also have common structural domains.

For example, TANGO 253 proteins, TANGO 257 proteins, INTERCEPT 258 proteins and TANGO 281 proteins of the invention have signal sequences. As used herein, a "signal sequence" includes a peptide of at least about 15 or 20 amino acid residues in length which occurs at the N-terminus of secretory and membrane-bound proteins and which contains at least about 70% hydrophobic amino acid residues such as alanine, leucine, isoleucine, phenylalanine, proline, tyrosine, tryptophan, or valine. In a preferred embodiment, a signal sequence contains at least about 10 to 40 amino acid residues, preferably about 19-34 amino acid residues, and has at least about 60-80%, more preferably 65-75%, and more preferably at least about 70% hydrophobic residues. A signal sequence serves to direct a protein containing such a sequence to a lipid bilayer. Thus, in one embodiment, a TANGO 253 protein contains a signal sequence of about amino acids 1 to 15 of SEQ ID NO:3 (SEQ ID NO:5) or about amino acids 1 to 15 of SEQ ID NO:10 (SEQ ID NO:12). In another embodiment, a TANGO 257 protein contains a signal sequence of about amino acids 1 to 21 of SEQ ID NO:17 (SEQ ID NO:19) or about amino acids 1 to 21 of SEQ ID NO:23 (SEQ ID NO:25). In another embodiment, an INTERCEPT 258 protein contains a signal sequence at about amino acids 1 to 29 of SEQ ID NO:28 (SEQ ID NO:30) or about amino acids 1 to 29 of SEQ ID NO:39 (SEQ ID NO:41). In yet another embodiment, a TANGO 281 protein contains a signal sequence of

about amino acids 1 to 38 of SEQ ID NO:48 (SEQ ID NO:49) or about amino acids 1 to 26 of SEQ ID NO:58 (SEQ ID NO:59). The signal sequence is cleaved during processing of the mature protein.

In one embodiment, TANGO 253 includes at least one RGD cell attachment site. An RGD domain contains a contiguous arginine-glycine-aspartic acid amino acid sequence and is involved in cell-cell, cell-extracellular matrix and cell adhesion interactions. In a preferred embodiment, a TANGO 253 family member has the amino acid sequence of SEQ ID NO:3 and, preferably, a RGD cell attachment site is located at about amino acid positions 77 to 79.

TANGO 253 family members can also include a collagen domain. As used herein, the term "collagen domain" refers to a protein domain containing a G-X-Y amino acid repeat motif, wherein the first amino acid residue is glycine and the second and third amino acid residues can be any residue but are preferably proline or hydroxyproline. Typically, a collagen domain contains at least about 3 to 5 G-X-Y repeats, and can contain about 3, 5, 8, 10, 12, 15, 20 or more continuous G-X-Y repeats. In one embodiment, a collagen domain can fold to form a triple helical structure.

In one embodiment, a TANGO 253 family member includes at least one collagen domain having an amino acid sequence that is at least about 40%, 50%, 60%, 70%, 80%, 90%, 95% or 98% identical to amino acids 36 to 95 of SEQ ID NO:3, which is the collagen domain of human TANGO 253 (SEQ ID NO:6), or amino acids 36 to 95 of SEQ ID NO:10, which is the collagen domain of mouse TANGO 253 (SEQ ID NO:13), while maintaining a glycine residue at the first position of G-X-Y repeats within the domain to maintain at least 3, 5, 8, 10, 12, 15 or 20 contiguous G-X-Y repeats, or while most preferably maintaining a glycine repeat at the first position of each G-X-Y repeat within the domain.

TANGO 253 family members can also include a C1q domain or at least one of the conserved amino acid motifs found therein. As used herein, the term "C1q domain" refers to a protein domain that bears homology to a C1q domain present within a member of the C1 enzyme complex. A C1q domain typically includes about 130-140 amino acid residues. C1q domains are utilized in processes involving, *e.g.*, correct protein folding and alignment and protein-protein interactions.

In one embodiment, a TANGO 253 family member includes one or more C1q domains having an amino acid sequence that is at least 45%, preferably about 50%, 55%, 60%, 70%, 75%, 80%, 90%, 95% and most preferably at least about 98% identical to amino acids 105 to 232 of SEQ ID NO:3, which is the human TANGO 253 C1q domain

(SEQ ID NO:7) or amino acids 105 to 232 of SEQ ID NO:10, which is the mouse TANGO 253 C1q domain (SEQ ID NO:14).

Embodiments of TANGO 253 family members include, but are not limited to, human, mouse and rat TANGO 253 nucleic acids and proteins. The features of the human and mouse TANGO 253 are described below. A cDNA encoding a rat TANGO 253 nucleotide sequence (SEQ ID NO:74), identified in clone jtrxa001e10t1, is 75.4% identical to human TANGO 253 (SEQ ID NO:1) in a 536 bp overlap. Further, the isolated rat TANGO 253 nucleotide sequence (SEQ ID NO:74) is 86% identical to mouse TANGO 253 (SEQ ID NO:9) in a 472 bp overlap.

Embodiments of TANGO 257 family members include, but are not limited to, human, mouse and rat TANGO 257 nucleic acids and proteins. The features of the human and mouse TANGO 257 are described below. A cDNA encoding a rat TANGO 257 nucleotide sequence (SEQ ID NO:75), identified within clone jtrxa102g06t1, is 83.8% identical to human TANGO 257 (SEQ ID NO:15) in a 734 bp overlap. Further, the isolated rat TANGO 257 nucleotide sequence (SEQ ID NO:75) is 88.4% identical to mouse TANGO 257 (SEQ ID NO:21) in a 731 bp overlap.

In one example, a TANGO 257 family member includes one or more of the following domains: (1) an extracellular domain; (2) a transmembrane domain; and (3) a cytoplasmic domain. In one embodiment, a TANGO 257 protein contains cytoplasmic domains of about amino residues 1 to 202 of SEQ ID NO:17 (SEQ ID NO:84) and about amino acid residues 338 to 406 of SEQ ID NO:17 (SEQ ID NO:92), transmembrane domains of about amino acid residues 203 to 221 of SEQ ID NO:17 (SEQ ID NO:86) and about amino acid residues 321 to 337 of SEQ ID NO:17 (SEQ ID NO:87), and an extracellular domain of about amino acid residues 222 to 320 of SEQ ID NO:17 (SEQ ID NO:88). In an alternative embodiment, a TANGO 257 protein contains an extracellular domain of about amino acid residues 1 to 320 of SEQ ID NO:17 (SEQ ID NO:89) or a mature extracellular domain of about amino acid residues 22 to 320 of SEQ ID NO:17 (SEQ ID NO:90), a transmembrane domain of about amino acid residues 321 to 337 of SEQ ID NO:17 (SEQ ID NO:87), and a cytoplasmic domain of about amino acid residues 338 to 406 of SEQ ID NO:17 (SEQ ID NO:92). In another embodiment, a mature TANGO 257 protein contains about amino acid residues 22 to 406 of SEQ ID NO:17 (SEQ ID NO:18).

In another embodiment, a TANGO 257 protein contains intracellular domains of about amino acid residues 1 to 202 of SEQ ID NO:23 (SEQ ID NO:93) and about amino acid residues 338 to 406 of SEQ ID NO:23 (SEQ ID NO:94), transmembrane domains of about amino acid residues 203 to 221 of SEQ ID NO:23 (SEQ ID NO:95) and about

amino acid residues 321 to 337 of SEQ ID NO:32 (SEQ ID NO:96), and an extracellular domain of about amino acid residues 222 to 320 of SEQ ID NO:23 (SEQ ID NO:97). In alternative embodiment, a TANGO 257 protein contains an extracellular domain of about amino acid residues 1 to 320 of SEQ ID NO:23 (SEQ ID NO:98) or a mature extracellular domain of about amino acid residues 22 to 320 of SEQ ID NO:23 (SEQ ID NO:99), a transmembrane domain of about amino acid residues 321 to 337 of SEQ ID NO:25 (SEQ ID NO:96), and an intracellular domain of about amino acid residues 338 to 406 of SEQ ID NO:23 (SEQ ID NO:94). In another embodiment, a mature TANGO 257 protein contains about amino acid residues 22 to 406 of SEQ ID NO:23 (SEQ ID NO:24).

In another example, an INTERCEPT 258 family member includes one or more of the following domains: (1) an extracellular domain; (2) a transmembrane domain; and (3) a cytoplasmic domain. Thus, in one embodiment, an INTERCEPT 258 protein contains extracellular domains of about amino acid residues 1 to 206 of SEQ ID NO:28 (SEQ ID NO:81) or about amino acid residues 30 to 206 of SEQ ID NO: 28 (SEQ ID NO:76) and about amino acid residues 272 to 370 of SEQ ID NO: 28 (SEQ ID NO:34), transmembrane domains of about amino acid residues 207 to 224 of SEQ ID NO:28 (SEQ ID NO:78) and about amino acid residues 247 to 271 of SEQ ID NO:28 (SEQ ID NO:33), and a cytoplasmic domain of about amino acid residues 225 to 246 of SEQ ID NO:28 (SEQ ID NO:79). In an alternative embodiment, an INTERCEPT 258 protein contains an extracellular domain of about amino acid residues 272 to 370 of SEQ ID NO:28 (SEQ ID NO:34), a transmembrane domain of about amino acid residues 247 to 271 of SEQ ID NO:28 (SEQ ID NO:33), and a cytoplasmic domain of about amino acid residues 1 to 246 of SEQ ID NO:28 (SEQ ID NO:31) or a mature cytoplasmic domain of about amino acid residues 30 to 246 of SEQ ID NO:28 (SEQ ID NO:82). In accordance with these embodiments, an INTERCEPT 258 protein is a mature protein containing an extracellular, transmembrane and cytoplasmic domain of about amino acids 30 to 370 of SEQ ID NO:28 (SEQ ID NO:29).

In another embodiment, an INTERCEPT 258 protein contains an extracellular domain of about amino acids 1 to 249 of SEQ ID NO:39 (SEQ ID NO:42), or a mature extracellular domain of about amino acids 30 to 249 of SEQ ID NO:39 (SEQ ID NO:83). In another embodiment, an INTERCEPT 258 protein contains a transmembrane domain of about amino acids 250 to 274 of SEQ ID NO:39 (SEQ ID NO:44). In another embodiment, an INTERCEPT 258 protein contains a cytoplasmic domain of about amino acids 275 to 394 of SEQ ID NO:39 (SEQ ID NO:45). In accordance with these embodiments, an INTERCEPT 258 protein is a mature protein containing an extracellular,

transmembrane and cytoplasmic domain of about 30 to 394 of SEQ ID NO:39 (SEQ ID NO:40).

INTERCEPT 258 family members can also include an immunoglobulin (Ig) domain contained within the extracellular domain. As used herein, the term "Ig domain" refers to a protein domain bearing homology to immunoglobulin superfamily members. An Ig domain includes about 30-90 amino acid residues, preferably about 40-80 amino acid residues, more preferably about 50-70 amino acid residues, still more preferably about 55-65 amino acid residues, and most preferably about 57 to 59 amino acid residues. In certain embodiments, an Ig domain contains a conserved cysteine residue within about 5 to 15 amino acid residues, preferably about 7 to 12 amino acid residues, and most preferably about 8 amino acid residues from its N-terminal end, and another conserved cysteine residue within about 1 to 5 amino acid residues, preferably about 2 to 4 amino acid residues, and most preferably about 3 amino acid residues from its C-terminal end.

An Ig domain typically has the following consensus sequence, beginning about 1 to 15 amino acid residues, more preferably about 3 to 10 amino acid residues, and most preferably about 5 amino acid residues from the C terminal end of the domain: (FY)-Xaa-C-Xaa-(VA)-COO-, wherein (FY) is either a phenylalanine or a tyrosine residue (preferably tyrosine), where "Xaa" is any amino acid, C is a cysteine residue, (VA) is either a valine or an alanine residue (preferably alanine), and COO- is the protein C terminus.

In one embodiment, an INTERCEPT 258 family member includes one or more Ig domains having an amino acid sequence that is at least about 55%, preferably at least about 65%, more preferably at least 75%, yet more preferably at least about 85%, and most preferably at least about 95% identical to amino acids 49 to 128 and/or amino acids 167 to 226 of SEQ ID NO:28, which are the Ig domains of human INTERCEPT 258 (these Ig domains are also represented as SEQ ID NO:35 and 36, respectively).

In another embodiment, an INTERCEPT 258 family member includes one or more Ig domains having an amino acid sequence that is at least about 55%, preferably at least about 65%, more preferably at least about 75%, yet more preferably at least about 85%, and most preferably at least about 95% identical to amino acids 167 to 226 of SEQ ID NO:28 (SEQ ID NO:36), includes a conserved cysteine residue about 8 residues downstream from the N-terminus of the Ig domain, and has one or more Ig domain consensus sequences described herein. In another embodiment, an INTERCEPT 258 family member includes one or more Ig domains having an amino acid sequence that is at least 55%, preferably at least about 65%, more preferably at least about 75%, yet more preferably at least about 85%, and most preferably at least about 95% identical to amino

acids 167 to 226 of SEQ ID NO:28 (SEQ ID NO:36), includes a conserved cysteine residue 8 residues downstream from the N-terminus of the Ig domain, has one or more Ig domain consensus sequences described herein, and has a conserved cysteine within the consensus sequence that forms a disulfide both with said first conserved cysteine. In yet another embodiment, an INTERCEPT 258 family member includes one or more Ig domains having an amino acid sequence that is at least 55%, preferably at least about 65%, more preferably at least about 75%, yet more preferably at least about 85%, and most preferably at least about 95% identical to amino acids 167 to 226 of SEQ ID NO:28 (SEQ ID NO:36), includes a conserved cysteine residue 8 residues downstream from the N-terminus of the Ig domain, has one or more Ig domain consensus sequences described herein, has a conserved cysteine within the consensus sequence that forms a disulfide both with said first conserved cysteine, and has at least one INTERCEPT 258 biological activity as described herein.

In a preferred embodiment, an INTERCEPT 258 family member has the amino acid sequence of SEQ ID NO:28 wherein the aforementioned Ig conserved residues are located as follows: the N-terminal conserved cysteine residue is located at about amino acid position 174 (within the Ig domain SEQ ID NO:36) and the C-terminal conserved cysteine is located at about amino acid position 224 (within the Ig domain SEQ ID NO:36).

In another embodiment, an INTERCEPT 258 family member includes one or more Ig domains having an amino acid sequence that is at least about 55%, preferably at least about 65%, more preferably at least about 75%, yet more preferably at least about 85%, and most preferably at least about 95% identical to amino acids 170 to 229 of SEQ ID NO:39, which is the Ig domain of mouse INTERCEPT 258 (SEQ ID NO:71). In another embodiment, an INTERCEPT 258 family member includes one or more Ig domains having an amino acid sequence that is at least about 55%, preferably at least about 65%, more preferably at least about 75%, yet more preferably at least about 85%, and most preferably at least about 95% identical to amino acids 170 to 229 of SEQ ID NO:39 (SEQ ID NO:71), includes a conserved cysteine residue about 8 residues downstream from the N-terminus of the Ig domain, and has one or more Ig domain consensus sequences described herein, has a conserved cysteine within the consensus sequence that forms a disulfide both with said first conserved cysteine, and has at least one INTERCEPT 258 biological activity as described herein.

In a preferred embodiment, an INTERCEPT 258 family member has the amino acid sequence of SEQ ID NO:39 wherein the aforementioned Ig domain conserved residues are located as follows: the N-terminal conserved cysteine residue is located at

about amino acid residue position 177 (within the Ig domain SEQ ID NO:71) and the C-terminal conserved cysteine residue is located at about amino acid position 227 (within the Ig domain SEQ ID NO:71).

In another example, a TANGO 281 family member consists of one or more of the following domains: (1) an extracellular domain; (2) a transmembrane domain; and (3) a cytoplasmic domain. In one embodiment, a TANGO 281 protein contains an extracellular domain at amino acids 1 to about 123 of SEQ ID NO:48 or a mature extracellular domain at about amino acid residues 39 to 123 of SEQ ID NO:48 (SEQ ID NO:51), a transmembrane domain at about amino acid residues 124 to 148 of SEQ ID NO:48 (SEQ ID NO:52), and a cytoplasmic domain at about amino acid residues 149 to 245 of SEQ ID NO:48 (SEQ ID NO:53). In another embodiment, a mature TANGO 281 protein contains about amino acid residues 39 to 245 of SEQ ID NO: 48 (SEQ ID NO: 50). In another embodiment, a TANGO 281 family contains an extracellular domain at amino acids 1 to about 112 of SEQ ID NO:58 or a mature extracellular domain at about amino acid residues 27 to 112 of SEQ ID NO:58 (SEQ ID NO:61), a transmembrane domain at about amino acid residues 113 to 137 of SEQ ID NO:78 (SEQ ID NO:62), and a cytoplasmic domain at about amino acid residues 138 to 213 of SEQ ID NO:78 (SEQ ID NO:63). In yet another embodiment, a mature TANGO 281 protein contains about amino acid residues 27 to 213 of SEQ ID NO: 58 (SEQ ID NO: 61).

In one embodiment, a TANGO 281 family member includes a signal sequence. In a preferred embodiment, a TANGO 281 family member has the amino acid sequence of SEQ ID NO:48, and the signal sequence is located at about amino acids 1 to 38. In an another preferred embodiment, a TANGO 281 family member has the amino acid sequence of SEQ ID NO:58, and the signal sequence is located at about amino acids 1 to 26.

A photosystem II 10kd phosphoprotein (PSBH) domain has been identified in the TANGO 281 proteins. The domain is also present in the chloroplast gene PSBH that encodes a 9-10kDa thylakoid membrane protein (PSII-H) which is associated with photosystem II. In one embodiment, a TANGO 281 family member includes one or more PSBH domains having an amino acid sequence that is at least about 55%, preferably at least about 65%, more preferably at least 75%, yet more preferably at least about 85%, and most preferably at least about 95% identical to amino acids 41 to 90 and/or amino acids 127 to 182 of SEQ ID NO:48, which are the PSBH domains of human TANGO 281 (these PSBH domains are also represented as SEQ ID NO:54 and 55, respectively). In another embodiment, a TANGO 281 family member includes one or more PSBH domains having an amino acid sequence that is at least about 55%, preferably at least about 65%, more

preferably at least about 75%, yet more preferably at least about 85%, and most preferably at least about 95% identical to amino acids 41 to 90 and/or amino acids 127 to 182 of SEQ ID NO:48, which are the PSBH domains of human TANGO 281 (these PSBH domains are also represented as SEQ ID NO:54 and 55, respectively), includes one or more PSBH domain consensus sequences described herein, and has at least one TANGO 281 biological activity as described herein.

In another embodiment, a TANGO 281 family member includes one or more PSBH domains having an amino acid sequence that is at least about 55%, preferably at least about 65%, more preferably at least 75%, yet more preferably at least about 85%, and most preferably at least about 95% to 98% identical to amino acids 42 to 91 and/or amino acids 128 to 183 of SEQ ID NO:58, which are the PSBH domains of mouse TANGO 281 (these PSBH domains are also represented as SEQ ID NO:64 and 65, respectively). In another embodiment, a TANGO 281 family member includes one or more PSBH domains having an amino acid sequence that is at least about 55%, preferably at least about 65%, more preferably at least about 75%, yet more preferably at least about 85%, and most preferably at least about 95% identical to amino acids 42 to 91 and/or amino acids 128 to 183 of SEQ ID NO:58, which are the PSBH domains of mouse TANGO 281 (these PSBH domains are also represented as SEQ ID NO:64 and 65, respectively), includes one or more PSBH domain consensus sequences described herein, and has at least one TANGO 281 biological activity as described herein.

Various features of human and mouse TANGO 253, TANGO 257, INTERCEPT 258 and TANGO 281 are summarized below.

Human TANGO 253

A cDNA encoding human TANGO 253 was identified by analyzing the sequences of clones present in a coronary artery smooth muscle library for sequences that encode secreted proteins. The primary cells utilized in construction of the library had been stimulated with agents that included phorbol 12-myristate 13-acetate (PMA), tumor neurosis factor (TNF), ionomycin, and cyclohexamide (CHX). This analysis led to the identification of a clone, Athma27h9, encoding full-length human TANGO 253. The human TANGO 253 cDNA of this clone is 1339 nucleotides long (Figures 1A-1B; SEQ ID NO:1). The open reading frame of this cDNA, nucleotides 188 to 916 of SEQ ID NO:1 (SEQ ID NO:2), encodes a 243 amino acid secreted protein (Figures 1A-1B; SEQ ID NO:3).

Figure 2 depicts a hydropathy plot of human TANGO 253. Relatively hydrophobic regions of the protein are shown above the horizontal line, and relatively

hydrophilic regions of the protein are below the horizontal line. The cysteine residues (cys) are indicated by short vertical lines just below the hydropathy trace. The dashed vertical line separates the signal sequence (amino acids 1 to 15 of SEQ ID NO:3; SEQ ID NO:5) on the left from the mature protein (amino acids 15 to 243 of SEQ ID NO:3; SEQ ID NO:4) on the right.

The signal peptide prediction program SIGNALP (Nielsen et al., 1997, *Protein Engineering* 10:1-6) predicted that human TANGO 253 includes a 15 amino acid signal peptide (amino acid 1 to amino acid 15 of SEQ ID NO:3; SEQ ID NO:5) preceding the mature human TANGO 253 protein (corresponding to amino acid 16 to amino acid 243 of SEQ ID NO:3; SEQ ID NO:4). The molecular weight of TANGO 253 protein without post-translational modifications is 25.3 kDa prior to the cleavage of the signal peptide, 23.8 kDa after cleavage of the signal peptide.

Human TANGO 253 includes a collagen domain (at about amino acids 36 to 95 of SEQ ID NO:3; SEQ ID NO:6) and a C1q domain (at about amino acids 105 to 232 of SEQ ID NO:3; SEQ ID NO:7) containing 23 G-X-Y repeats. An RGD cell attachment site is found at amino acids 77 to 79 of SEQ ID NO:3.

Three protein kinase C phosphorylation sites are present in human TANGO 253. The first has the sequence SAK (at amino acids 107 to 109 of SEQ ID NO:3), the second has the sequence TGK (at amino acids 140 to 142 of SEQ ID NO:3), and the third has the sequence SIK (at amino acids 220 to 222 of SEQ ID NO:3). Human TANGO 253 has three N-myristylation sites. The first has the sequence GLAAGS (at amino acids 11 to 16 of SEQ ID NO:3), the second has the sequence GGRPGL (at amino acids 68 to 73 of SEQ ID NO:3) and the third has the sequence GIYASI (at amino acids 216 to 221 of SEQ ID NO:3).

Northern analysis of human TANGO 253 expression demonstrates strong expression in heart, lung, liver, kidney and pancreas, and moderate expression in brain, placenta and skeletal muscle. Liver expression reveals two human TANGO mRNA bands, one of approximately 1.3kb (which is the size observed in the other tissues) as well as a band at approximately 1kb, which may be the result of an alternative splicing event.

Secretion assays reveal a human TANGO 253 protein of approximately 30kDa. The secretion assays were performed as follows: 8×10^5 293T cells were plated per well in a 6-well plate and the cells were incubated in growth medium (DMEM, 10% fetal bovine serum, penicillin/strepomycin) at 37°C, 5% CO_2 overnight. 293T cells were transfected with 2 μg of full-length TANGO 253 inserted in the pMET7 vector/well and 10 μg LipofectAMINE (GIBCO/BRL Cat. # 18324-012) /well according to the protocol for GIBCO/BRL LipofectAMINE. The transfectant was removed 5 hours later and fresh

growth medium was added to allow the cells to recover overnight. The medium was removed and each well was gently washed twice with DMEM without methionine and cysteine (ICN Cat. # 16-424-54). 1 ml DMEM without methionine and cysteine with 50 μCi Trans-^{35}S (ICN Cat. # 51006) was added to each well and the cells were incubated at 37°C, 5% CO_2 for the appropriate time period. A 150 μl aliquot of conditioned medium was obtained and 150 μl of 2X SDS sample buffer was added to the aliquot. The sample was heat-inactivated and loaded on a 4-20% SDS-PAGE gel. The gel was fixed and the presence of secreted protein was detected by autoradiography.

TANGO 253 exhibits homology to an adipocyte complement-mediated protein precursor and so may be involved in adipocyte function, *e.g.*, may act as a signaling molecule for adipocyte tissue. Figure 6A shows an alignment of the human TANGO 253 amino acid sequence (SEQ ID NO:3) with the human adipocyte complement-mediated protein precursor amino acid sequence (SEQ ID NO:20). The alignment shows that there is a 38.7% overall amino acid sequence identity between human TANGO 253 and human adipocyte complement-mediated protein precursor.

Figures 7A-7C shows an alignment of the nucleotide sequence of human adipocyte complement-mediated protein precursor nucleotide sequence (SEQ ID NO:32); GenBank Accession Number A1417523) and the nucleotide sequence of human TANGO 253 (SEQ ID NO:1). The alignment shows a 29.1% overall sequence identity between the two nucleotide sequences.

The human TANGO 253 nucleotide sequence was mapped to human chromosome 11, between flanking markers D11S1356 and D11S924 using the Genebridge 4 Human Radiation hybrid mapping panel with CAAAGTGAGCTCATGCTCTCAC (SEQ ID NO:193) as the forward primer and CTCTGGTCTTGGGCAGAAATC (SEQ ID NO:194) as the reverse primer.

Clone EpT253, which encodes human TANGO 253, was deposited with the American Type Culture Collection (10801 University Boulevard, Manassas, VA 20110-2209) on April 21, 1999 and assigned Accession Number 207222. This deposit will be maintained under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. This deposit was made merely as a convenience for those of skill in the art and is not an admission that a deposit is required under 35 U.S.C. §112.

Mouse TANGO 253

A cDNA encoding mouse TANGO 253 was identified by analyzing the sequences of clones present in a mouse microglia library using a rat TANGO 253 probe from sciatic

nerve. This analysis led to the identification of a clone, AtmXa1e1075, encoding full-length mouse TANGO 253. The mouse TANGO 253 cDNA of this clone is 1263 nucleotides long (Figures 3A-3B; SEQ ID NO:8). The open reading frame of this cDNA, nucleotides 135 to 863 of SEQ ID NO:8 (SEQ ID NO:9), encodes a 243 amino acid secreted protein (Figures 3A-3B; SEQ ID NO:10).

Figure 4 depicts a hydropathy plot of mouse TANGO 253. Relatively hydrophobic regions of the protein are shown above the horizontal line, and relatively hydrophilic regions of the protein are below the horizontal line. The cysteine residues (cys) are indicated by short vertical lines just below the hydropathy trace. The dashed vertical line separates the signal sequence (amino acid 1 to amino acid 15 of SEQ ID NO:10; SEQ ID NO:12) on the left from the mature protein (amino acid 16 to amino acid 243 of SEQ ID NO:10; SEQ ID NO:11) on the right.

The signal peptide prediction program SIGNALP (Nielsen et al., 1997, Protein Engineering 10:1-6) predicted that mouse TANGO 253 includes a 15 amino acid signal peptide (amino acid 1 to amino acid 15 of SEQ ID NO:10; SEQ ID NO:12) preceding the mature mouse TANGO 253 protein (corresponding to amino acid 16 to amino acid 243 of SEQ ID NO:10; SEQ ID NO:11). The molecular weight of mouse TANGO 253 protein without post-translational modifications is 25.4 kDa prior to the cleavage of the signal peptide, 23.9 kDa after cleavage of the signal peptide.

Mouse TANGO 253 includes a collagen domain (at amino acids 36 to 95 of SEQ ID NO:10; SEQ ID NO:13) and a C1q domain (at amino acids 105-232 of SEQ ID NO:10; SEQ ID NO:14).

Three protein kinase C phosphorylation sites are present in mouse TANGO 253. The first has the sequence SAK (at amino acids 107 to 109 of SEQ ID NO:10), the second has the sequence TGK (at amino acids 140 to 142 of SEQ ID NO:10), and the third has the sequence SIK (at amino acids 220 to 222 of SEQ ID NO:10). Mouse TANGO 253 has four N-myristylation sites. The first has the sequence GLVSGS (at amino acids 11 to 16 of SEQ ID NO:10), the second has the sequence GGRPGL (at amino acids 68 to 73 of SEQ ID NO:10), the third has the sequence GQSIAS (at amino acids 172 to 177 of SEQ ID NO:10), and the fourth has the sequence GIYASI (at amino acids 216 to 221 of SEQ ID NO:10).

As shown in Figure 5, human TANGO 253 protein and mouse TANGO 253 protein are 93.8% identical. Figure 6B shows an alignment of the mouse TANGO 253 amino acid sequence (SEQ ID NO:10) with the human adipocyte complement-mediated protein precursor amino acid sequence (SEQ ID NO:20). The alignment shows that there

is a 38.3% overall amino acid sequence identity between mouse TANGO 253 and human adipocyte complement-mediated protein precursor.

Figures 8A-8C shows an alignment of the nucleotide sequence of human adipocyte complement-mediated protein precursor nucleotide sequence (SEQ ID NO:32); GenBank Accession Number A1417523) and the nucleotide sequence of mouse TANGO 253 (SEQ ID NO:8). The alignment shows a 30.4% overall sequence identity between the two nucleotide sequences.

In situ tissue screening was performed on mouse embryonic tissue (obtained from embryos at embryonic day 13.5 to postnatal day 1.5) and adult tissue to determine the expression of mouse TANGO 253 mRNA. Expression of mouse TANGO 253 during embryogenesis was ubiquitously expressed throughout the central nervous system. Strong expression of mouse TANGO 253 was detected in choriod plexus of the fourth ventricle of E18.5 and E1.5 embryos examined. Expression of mouse TANGO 253 was also detected in the lungs of E14.5 and E15.5 embryos and in the kidneys of E15.5 embryos.

Mouse TANGO 253 expression was detected by *in situ* hybridization in the following adult tissues: a signal was detected in the brain in the choroid plexus of the lateral and 4th ventricles, and the olfactory bulb; a signal was detected in the cortical region of the kidney consistent with the pattern of glomeruli (in particular, the cortical radial veins); a ubiquitous signal was detected in the thymus; a weak, ubiquitous signal was detected in the spleen; a moderate signal was associated with the seminiferous vesicles of the testes; a signal was detected in the ovaries; and a ubiquitous signal restricted to the zone of giant cells was detected in the placenta.

Clone EpTm253, which encodes mouse TANGO 253, was deposited with the American Type Culture Collection (10801 University Boulevard, Manassas, VA 20110-2209) on April 21, 1999 and assigned Accession Number 207215. This deposit will be maintained under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. This deposit was made merely as a convenience for those of skill in the art and is not an admission that a deposit is required under 35 U.S.C. §112.

Uses of TANGO 253 Nucleic acids, Polypeptides, and Modulators Thereof

As TANGO 253 was originally found in the coronary artery smooth muscle library described above, TANGO 253 nucleic acids, proteins, and modulators thereof can be used to modulate the proliferation, development, differentiation, and/or function of organs, *e.g.*, tissues and cells that form blood vessels and coronary tissue, *e.g.*, cells of the coronary connective tissue, *e.g.*, abnormal coronary smooth muscle cells and/or endothelial cells of

blood vessels. TANGO 253 nucleic acids, proteins, and modulators thereof can also be used to modulate symptoms associated with abnormal coronary function, *e.g.*, heart diseases and disorders such as atherosclerosis, coronary artery disease and plaque formation.

In light of the collagen domain, TANGO 253 nucleic acids, proteins and modulators thereof can be utilized to modulate (*e.g.*, stabilize, promote, inhibit or disrupt) cell/extracellular matrix (ECM) interactions, cell/cell interactions and, for example, signal transduction events associated with such interactions. For example, such TANGO 253 compositions and modulators thereof can be used to modulate binding of such ECM-associated factors as integrin and can function to modulate ligand binding to cell surface receptors. In addition, TANGO 253 nucleic acids, proteins and modulators thereof can be utilized to modulate connective tissue formation, maintenance and function, as well as to modulate symptoms associated with connective tissue-related disorders, to promote wound healing, and to reduce, slow or inhibit ameliorate connective tissue-related signs of aging, such as wrinkle formation.

In light of the C1q domain exhibited by TANGO 253 proteins and their similarity to the collectin family, TANGO 253 nucleic acids, proteins and modulators thereof can be utilized to modulate immune-related processes such as the ability to modulate host immune response by, *e.g.*, modulating one or more elements in the serum complement cascade, including, for example activation of the cascade, formation of and/or binding to immune complexes, detection and defense against surface antigens and bacteria, and immune surveillance for rapid removal or pathogens. Such TANGO 253 compositions and modulators thereof can be utilized, *e.g.*, to ameliorate incidence of any symptoms associated with disorders that involve such immune-related processes, including, but not limited to infection and autoimmune disorders.

In addition, such compositions and modulators thereof can be utilized to modulate folding and alignment of the collagen domain (*e.g.*, into a triple helix), disorders associated with collagen defects, including but not limited to bone disorders, *e.g.*, bone resorption disorders, or hearing, *e.g.*, inner ear, disorders, to modulate protein-protein interactions and recognition events (either homotypic or heterotypic) and cellular response events (*e.g.*, signal transduction events) associated with such interactions and recognitions, and to ameliorate symptoms associated with abnormal signaling, protein-protein interaction and/or cellular response events including, but not limited to cell proliferation disorders such as cancer, abnormal neuronal interactions, such as disorders involving abnormal synaptic activity, *e.g.*, abnormal Purkinje cell activities.

Human TANGO 253 protein contains an RGD domain. As such, TANGO 253 nucleic acids, proteins and modulators thereof can be utilized to modulate processes involved in, *e.g.*, bone development, sepsis, tumor progression, metastasis, cell migration, fertilization, and cellular interactions with the extracellular matrix required for growth, differentiation, and apoptosis, as well as cellular processes involving cell adhesion, such as cell migration.

TANGO 253 proteins exhibit similarity to adipocyte complement-related protein precursor and can act as signaling molecules for adipocyte tissue. In light of this, TANGO 253 nucleic acids, proteins and modulators thereof can be utilized to modulate adipocyte function and adipocyte-related processes and disorders such as, *e.g.*, obesity.

TANGO 253 nucleic acids, proteins, and modulators thereof can also be utilized to modulate the development, differentiation, maturation, proliferation and/or activity of cells of the central nervous system such as neurons, glial cells (*e.g.*, astrocytes and oligodendrocytes), and Schwann cells. TANGO 253 nucleic acids, polypeptides, or modulators thereof can also be used to treat disorders of the brain, such as cerebral edema, hydrocephalus, brain herniations, iatrogenic disease (due to, *e.g.*, infection, toxins, or drugs), inflammations (*e.g.*, bacterial and viral meningitis, encephalitis, and cerebral toxoplasmosis), cerebrovascular diseases (*e.g.*, hypoxia, ischemia, and infarction, intracranial hemorrhage and vascular malformations, and hypertensive encephalopathy), tumors (*e.g.*, neuroglial tumors, neuronal tumors, tumors of pineal cells, meningeal tumors, primary and secondary lymphomas, intracranial tumors, and medulloblastoma), and to treat injury or trauma to the brain.

TANGO 253 nucleic acids, proteins, and modulators thereof can also be utilized to treat renal (kidney) disorders, such as glomerular diseases (*e.g.*, acute and chronic glomerulonephritis, rapidly progressive glomerulonephritis, nephrotic syndrome, focal proliferative glomerulonephritis, glomerular lesions associated with systemic disease, such as systemic lupus erythematosus, Goodpasture's syndrome, multiple myeloma, diabetes, polycystic kidney disease, neoplasia, sickle cell disease, and chronic inflammatory diseases), tubular diseases (*e.g.*, acute tubular necrosis and acute renal failure, polycystic renal diseasemedullary sponge kidney, medullary cystic disease, nephrogenic diabetes, and renal tubular acidosis), tubulointerstitial diseases (*e.g.*, pyelonephritis, drug and toxin induced tubulointerstitial nephritis, hypercalcemic nephropathy, and hypokalemic nephropathy), acute and rapidly progressive renal failure, chronic renal failure, nephrolithiasis, gout, vascular diseases (*e.g.*, hypertension and nephrosclerosis, microangiopathic hemolytic anemia, atheroembolic renal disease, diffuse cortical necrosis, and renal infarcts), or tumors (*e.g.*, renal cell carcinoma and nephroblastoma).

TANGO 253 nucleic acids, proteins and modulators thereof can, in addition to the above, be utilized to regulate or modulate development and/or differentiation of processes involved in microglial, lung, liver, kidney, pancreas, brain, placental and skeletal muscle formation and activity, as well as in ameliorating any symptom associated with a disorder of such cell types, tissues and organs.

TANGO 253 expression can be utilized as a marker (*e.g.*, an *in situ* marker) for specific tissues (*e.g.*, the brain) and/or cells (*e.g.*, neurons) in which TANGO 253 is expressed. TANGO 253 nucleic acids can also be utilized for chromosomal mapping.

<u>Human TANGO 257</u>

A cDNA encoding human TANGO 257 was identified by analyzing the sequences of clones present in a coronary smooth muscle library for sequences that encode secreted proteins. This analysis led to the identification of a clone, Athma7c10, encoding full-length human TANGO 257. The human TANGO 257 cDNA of this clone is 1832 nucleotides long (Figures 9A-9B; SEQ ID NO:15). The open reading frame of this cDNA, nucleotides 88 to 1305 of SEQ ID NO:15 (SEQ ID NO:16), encodes a 406 amino acid secreted protein (Figures 9A-9B; SEQ ID NO:17).

Figure 10 depicts a hydropathy plot of human TANGO 257. Relatively hydrophobic regions of the protein are above the horizontal line, and relatively hydrophilic regions of the protein are below the horizontal line. The cysteine residues (cys) and N-glycosylation sites are (Ngly) are indicated by short vertical lines just below the hydropathy trace. The dashed vertical line separates the signal sequence from the mature protein described below.

The signal peptide prediction program SIGNALP (Nielsen et al., 1997, *Protein Engineering* <u>10</u>:1-6) predicted that human TANGO 257 includes a 21 amino acid signal peptide (amino acid 1 to amino acid 21 of SEQ ID NO:17; SEQ ID NO:19) preceding the mature human TANGO 257 protein (corresponding to amino acid 22 to amino acid 406 of SEQ ID NO:17; SEQ ID NO:18). The molecular weight of human TANGO 257 protein without post-translational modifications is 46.0 kDa prior to the cleavage of the signal peptide, 43.8 kDa after cleavage of the signal peptide.

Two N-glycosylation sites are present in human TANGO 257. The first has the sequence NDTA and is found at amino acids 177 to 180 of SEQ ID NO:17, and the second has the sequence NRTV and is found at amino acids 248 to 251 of SEQ ID NO:17. A cAMP and cGMP dependent protein kinase phosphorylation site having the sequence RKAS is found in human TANGO 257 at amino acids 196 to 199 of SEQ ID NO:17. Five protein kinase C phosphorylation sites are present in human TANGO 257. The first has

the sequence SSR (at amino acids 48 to 50 of SEQ ID NO:17), the second has the sequence SGR (at amino acids 84 to 86 of SEQ ID NO:17), the third has the sequence SMK (at amino acids 144 to 146 of SEQ ID NO:17), the fourth has the sequence TEK (at amino acids 166 to 168 of SEQ ID NO:17) and the fifth has the sequence SLR (at amino acids 374 to 376 of SEQ ID NO:17). Five casein kinase II phosphorylation sites are present in human TANGO 257. The first has the sequence TEAD (at amino acids 78 to 81 of SEQ ID NO:17), the second has the sequence TQND (at amino acids 175 to 178 of SEQ ID NO:17), the third has the sequence TVVD (at amino acids 250 to 253 of SEQ ID NO:17), the fourth has the sequence TYID (at amino acids 272 to 275 of SEQ ID NO:17), and the fifth has the sequence TRED (at amino acids 289 to 292 of SEQ ID NO:17). Human TANGO 257 has a tyrosine kinase phosphorylation site having the sequence RLEREVDY at amino acids 89 to 96 of SEQ ID NO:17). Human TANGO 257 has three N-myristylation sites. The first has the sequence GGPGTK (at amino acids 115 to 120 of SEQ ID NO:17), the second has the sequence GGPAGL (at amino acids 152 to 157 of SEQ ID NO:17) and the third has the sequence GAHASL (at amino acids 370 to 375 of SEQ ID NO:17). Human TANGO 257 has an amidation site having the sequence KGRR at amino acids 122 to 125 of SEQ ID NO:17.

Northern analysis of human TANGO 257 expression demonstrates moderate expression in heart, liver and pancreas, and low expression in kidney, lung and skeletal muscle.

Secretion assays reveal a human TANGO 257 protein of approximately 50kDa. The secretion assays were performed as described in the human TANGO 253 section above.

The human TANGO 257 nucleotide sequence was mapped to human chromosome 1 using the Genebridge 4 Human Radiation hybrid mapping panel with GGATGATGG CTACCAGATTGTC (SEQ ID NO:195) as the forward primer and GGAACATTGAGGGTTTTGACTC (SEQ ID NO:196) as the reverse primer.

TANGO 257 is homologous to a protein encoded by a nucleic acid sequence referred to in PCT Publication WO 98/39446 as "gene 64". Figure 14 shows an alignment of the human TANGO 257 amino acid sequence (SEQ ID NO:17) with the gene 64 encoded amino acid sequence (SEQ ID NO:43). As shown in the figure, the 353 amino acid gene 64 polypeptide is identical to amino acid residues 1-353 of human TANGO 257 (SEQ ID NO:17). Human TANGO 257 contains 406 amino acids, *i.e.*, contains an additional 53 amino acid residues carboxy to residue 353. The overall amino acid sequence identity between full-length human TANGO 257 polypeptide and the gene 64-encoded polypeptide is approximately 87%.

Figures 15A-15D show an alignment of the nucleotide sequence of gene 64 (SEQ ID NO:66; PCT Publication WO 98/39446) and the nucleotide sequence of human TANGO 257 (SEQ ID NO:15). The nucleotide sequences of gene 64 and human TANGO 257 are 93.5% identical. Among the differences between the sequences is a cytosine nucleotide at human TANGO 257 (SEQ ID NO:15) position 1587 that represents an insertion relative to the corresponding gene 64 position when the gene 64 and TANGO 257 sequences are aligned. This additional cytosine results in the TANGO 257 open reading frame being 1218 base pairs encoding a polypeptide of 406 amino acid residues. In contrast, the gene 64 nucleic acid sequence encodes a polypeptide of only 353 amino acid residues, as discussed above.

Clone EpT257, which encodes human TANGO 257, was deposited with the American Type Culture Collection (10801 University Boulevard, Manassas, VA 20110-2209) on April 21, 1999 and assigned Accession Number 207222. This deposit will be maintained under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. This deposit was made merely as a convenience for those of skill in the art and is not an admission that a deposit is required under 35 U.S.C. §112.

Mouse TANGO 257

A cDNA encoding mouse TANGO 257 was identified by analyzing the sequences of clones present in a mouse microglia library using a rat TANGO 257 probe. This analysis led to the identification of a clone, Atmua102gbl, encoding full-length mouse TANGO 257. The mouse TANGO 257 cDNA of this clone is 1721 nucleotides long (Figures 11A-11B; SEQ ID NO:21). The open reading frame of this cDNA, nucleotides 31 to 1248 of SEQ ID NO:21 (SEQ ID NO:22), encodes a 406 amino acid secreted protein (Figures 11A-11B; SEQ ID NO:23).

Figure 12 depicts a hydropathy plot of mouse TANGO 257. Relatively hydrophobic regions of the protein are above the horizontal line, relatively hydrophilic regions of the protein are below the horizontal line. The cysteine residues (cys) and N-glycosylation sites are (Ngly) are indicated by short vertical lines just below the hydropathy trace. The dashed vertical line separates the signal sequence from the mature protein described below.

The signal peptide prediction program SIGNALP (Nielsen et al., 1997, Protein Engineering 10:1-6) predicted that mouse TANGO 257 includes a 21 amino acid signal peptide (amino acid 1 to amino acid 21 of SEQ ID NO:23; SEQ ID NO:25) preceding the mature TANGO 257 protein (corresponding to amino acid 22 to amino acid 406 of SEQ

ID NO:23; (SEQ ID NO:24). The molecular weight of mouse TANGO 257 protein without post-translational modifications is 45.8 kDa prior to the cleavage of the signal peptide, 43.6 kDa after cleavage of the signal peptide.

Two N-glycosylation sites are present in mouse TANGO 257. The first has the sequence NDTA and is found at amino acids 177 to 180 of SEQ ID NO:23, and the second has the sequence NRTV and is found at amino acids 248 to 251 of SEQ ID NO:23. A cAMP and cGMP-dependent protein kinase phosphorylation site having the sequence RKAS is found in mouse TANGO 257 at amino acids 196 to 199 of SEQ ID NO:23. Five protein kinase C phosphorylation sites are present in mouse TANGO 257. The first has the sequence SSR (at amino acids 48 to 50 of SEQ ID NO:23), the second has the sequence TLR (at amino acids 75 to 77 of SEQ ID NO:23), the third has the sequence SGR (at amino acids 84 to 86 of SEQ ID NO:23), the fourth has the sequence SMK (at amino acids 144 to 146 of SEQ ID NO:23) and the fifth has the sequence SLR (at amino acids 374 to 376 of SEQ ID NO:23). Five casein kinase II phosphorylation sites are present in mouse TANGO 257. The first has the sequence TEAD (at amino acids 78 to 81 of SEQ ID NO:23), the second has the sequence TQND (at amino acids 175 to 178 of SEQ ID NO:23), the third has the sequence TVVD (at amino acids 250 to 253 of SEQ ID NO:23), the fourth has the sequence TYID (at amino acids 272 to 275 of SEQ ID NO:23), and the fifth has the sequence TRRD (at amino acids 289 to 292 of SEQ ID NO:23). Mouse TANGO 257 has a tyrosine kinase phosphorylation site having the sequence RLEREVDY at amino acids 89 to 96 of SEQ ID NO:23. Mouse TANGO 257 has four N-myristylation sites. The first has the sequence GGPGAK (at amino acids 115 to 120 of SEQ ID NO:23), the second has the sequence GGSVGL (at amino acids 151 to 157 of SEQ ID NO:23), the third has the sequence GGPGGG (at amino acids 227 to 232 of SEQ ID NO:23), and the fourth has the sequence GAHASL (at amino acids 370 to 375 of SEQ ID NO:23). Mouse TANGO 257 has an amidation site having the sequence KGRR at amino acids 122 to 125 of SEQ ID NO:23.

As shown in Figure 13, human TANGO 257 protein and mouse TANGO 257 protein are 94.1% identical.

Figure 16 shows an alignment of mouse TANGO 257 amino acid sequence (SEQ ID NO:23) with the amino acid sequence encoded by gene 64 (SEQ ID NO:43). As shown in the figure, the 253 amino acid gene 64 polypeptide and the 406 amino acid mouse TANGO 257 polypeptide and the 406 amino acid mouse TANGO 257 polypeptide are approximately 82% identical. Figures 17A-17C show an alignment of the nucleotide sequence of gene 64 (SEQ ID NO:66; PCT publication no. 98/39446) and the nucleotide

sequence of mouse TANGO 257 (SEQ ID NO:21). As shown in the figure, the two nucleotide sequences are approximately 76% identical.

In situ tissue screening was performed on mouse adult tissues and embryonic tissues (obtained from embryos E13.5 to P1.5) to analyze for the expression of mouse TANGO 257 mRNA. Mouse TANGO 257 expression was detected the following adult tissues: the submandibular gland; the renal papilla region of the kidney; the capsule region of the adrenal gland; and the labyrinth zone of the placenta.

In the case of embryonic expression, mouse TANGO 257 expression was detected in the bones, lungs, intestines, and kidneys. At E13.5, a signal was detected in many tissues including the developing bone structures such as the vertebrae, of the spinal column, jaw, and scapula. At E14.5, the signal pattern was very similar to that detected at E13.5. At 15.5, a signal was detected in all major bone structures, including the skull, basisphenoid bone, upper and lower incisor teeth, vertebral column, sternum, scapula, and femur. A ubiquitous signal was also detected in the lung, kidney, and intestinal tract. At 16.5 and 18.5, the signal is very similar to that detected at E15.5. At P1.5, a signal was still detected in all of the major bone structures and signal detected in the lung, kidney, and intestines has dropped to nearly background levels.

Clone EpTm257, which encodes mouse TANGO 257, was deposited with the American Type Culture Collection (10801 University Boulevard, Manassas, VA 20110-2209) on April 21, 1999 and assigned Accession Number 207117. This deposit will be maintained under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. This deposit was made merely as a convenience for those of skill in the art and is not an admission that a deposit is required under 35 U.S.C. §112.

Uses of TANGO 257 Nucleic acids, Polypeptides, and Modulators Thereof

As TANGO 257 was originally found in a coronary artery smooth muscle library, TANGO 257 nucleic acids, proteins, and modulators thereof can be used to modulate the proliferation, development, differentiation, and/or function of organs, *e.g.*, heart, tissues and cells that form blood vessels and coronary tissue, *e.g.*, cells of the coronary connective tissue, *e.g.*, coronary smooth muscle cells and/or endothelial cells of blood vessels. TANGO 257 nucleic acids, proteins, and modulators thereof can also be used to modulate symptoms associated with abnormal coronary function, *e.g.*, heart diseases and disorders such as atherosclerosis, coronary artery disease and plaque formation.

In light of TANGO 257's homology to the extracellular molecule olfactomedin, TANGO 257 nucleic acids, proteins and modulators thereof can be utilized to modulate

development, differentiation, proliferation and/or activity of neuronal cells, *e.g.*, olfactory neurons and to modulate neuronal activities involving maintenance, growth and/or differentiation of chemosensory cilia, modulate cell-cell interactions and cell-ECM interactions, *e.g.*, neuronal (such as olfactory) cell-ECM interactions. TANGO 257 nucleic acids, proteins and modulations thereof can also be used to modulate symptoms associated with abnormal processes involving such cells and/or activities, for example neuronal function, *e.g.*, neurological disorders, neurodegenerative disorders, neuromuscular disorders, cognitive disorders, personality disorders, and motor disorders, and chemosensory disorders, such as olfactory-related disorders.

TANGO 257 exhibits homology to a gene referred to as "gene 64" (PCT Publication No. WO 98/39446), which is expressed primarily in fetal lung tissue. In light of this, TANGO 257 nucleic acids, proteins and modulators thereof can also be used to modulate development, differentiation, proliferation and/or activity of pulmonary system cells, *e.g.*, lung cell types, and to modulate a symptom associated with disorders of pulmonary development, differentiation and/or activity, *e.g.*, cystic fibrosis. TANGO 257 nucleic acids, proteins and modulators thereof can also be used to modulate symptoms associated with abnormal pulmonary development or function, such as lung diseases or disorders associated with abnormal pulmonary development or function, *e.g.*, cystic fibrosis. TANGO 257 nucleic acids, polypeptides, or modulators thereof can be used to treat pulmonary (lung) disorders, such as atelectasis, cystic fibrosis, rheumatoid lung disease, pulmonary congestion or edema, chronic obstructive airway disease (*e.g.*, emphysema, chronic bronchitis, bronchial asthma, and bronchiectasis), diffuse interstitial diseases (*e.g.*, sarcoidosis, pneumoconiosis, hypersensitivity pneumonitis, bronchiolitis, Goodpasture's syndrome, idiopathic pulmonary fibrosis, idiopathic pulmonary hemosiderosis, pulmonary alveolar proteinosis, desquamative interstitial pneumonitis, chronic interstitial pneumonia, fibrosing alveolitis, hamman-rich syndrome, pulmonary eosinophilia, diffuse interstitial fibrosis, Wegener's granulomatosis, lymphomatoid granulomatosis, and lipid pneumonia), or tumors (*e.g.*, bronchogenic carcinoma, bronchiolovlveolar carcinoma, bronchial carcinoid, hamartoma, and mesenchymal tumors).

TANGO 257 nucleic acids, proteins and modulators thereof can also be used to modulate cell proliferation, *e.g.*, abnormal cell proliferation. Such modulation may, for example, be via modulation of one or more elements involved in signal transduction cascades.

TANGO 257 nucleic acids, proteins and modulators thereof can also be utilized to modulate the development, differentiation, maturation, proliferation and/or activity of

bone cells such as osteocytes, and to treat bone associated diseases or disorders. Examples of bone diseases and disorders include bone injury due to for example, trauma (*e.g.*, bone breakage, cartilage tearing), degeneration (*e.g.*, osteoporosis), degeneration of joints, *e.g.*, arthritis, e.g., osteoarthritis, and bone wearing. Further, TANGO 257 nucleic acids, proteins and modulators thereof can be utilized to modulate or regulate the development of bone structures such as the skull, the basisphenoid bone, the upper and lower incisor teeth, the vertebral column, the sternum, the scapula, and the femur during embryogenesis.

TANGO 257 nucleic acids, proteins and modulators thereof can, in addition to the above, be utilized to regulate or modulate development and/or differentiation of processes involved in microglial, liver, kidney, and skeletal muscle formation and activity, as well as in ameliorating a symptom associated with a disorder of such cell types, tissues and organs.

TANGO 257 nucleic acids, polypeptides, or modulators thereof can also be used to treat renal (kidney) disorders, such as glomerular diseases (*e.g.*, acute and chronic glomerulonephritis, rapidly progressive glomerulonephritis, nephrotic syndrome, focal proliferative glomerulonephritis, glomerular lesions associated with systemic disease, such as systemic lupus erythematosus, Goodpasture's syndrome, multiple myeloma, diabetes, polycystic kidney disease, neoplasia, sickle cell disease, and chronic inflammatory diseases), tubular diseases (*e.g.*, acute tubular necrosis and acute renal failure, polycystic renal diseasemedullary sponge kidney, medullary cystic disease, nephrogenic diabetes, and renal tubular acidosis), tubulointerstitial diseases (*e.g.*, pyelonephritis, drug and toxin induced tubulointerstitial nephritis, hypercalcemic nephropathy, and hypokalemic nephropathy), acute and rapidly progressive renal failure, chronic renal failure, nephrolithiasis, gout, vascular diseases (*e.g.*, hypertension and nephrosclerosis, microangiopathic hemolytic anemia, atheroembolic renal disease, diffuse cortical necrosis, and renal infarcts), or tumors (*e.g.*, renal cell carcinoma and nephroblastoma). TANGO 257 polypeptides, nucleic acids, or modulators thereof can be used to treat intestinal disorders, such as ischemic bowel disease, infective enterocolitis, Crohn's disease, benign tumors, malignant tumors (*e.g.*, argentaffinomas, lymphomas, adenocarcinomas, and sarcomas), malabsorption syndromes (*e.g.*, celiac disease, tropical sprue, Whipple's disease, and abetalipoproteinemia), obstructive lesions, hernias, intestinal adhesions, intussusception, or volvulus.

Further, TANGO 257 expression can be utilized as a marker (*e.g.* an *in situ* marker) for specific tissues (*i.e.*, bone structures) and/or cells (*i.e.*, osteocytes) in which TANGO 257 is expressed. TANGO 257 nucleic acids can also be used for chromosomal mapping.

Human INTERCEPT 258

A cDNA encoding human INTERCEPT 258 was identified by analyzing the sequences of clones present in a human mixed lymphocyte reaction library for sequences that encode secreted proteins. This analysis led to the identification of a clone, Athlxtce, encoding full-length human INTERCEPT 258. The human INTERCEPT 258 cDNA of this clone is 1869 nucleotides long (Figures 18A-18B; SEQ ID NO:26). The open reading frame of this cDNA, nucleotides 153 to 1262 of SEQ ID NO:26 (SEQ ID NO:27), encodes a 370 amino acid transmembrane protein (Figures 18A-18B; SEQ ID NO:28).

Figure 19 depicts a hydropathy plot of human INTERCEPT 258. Relatively hydrophobic regions of the protein are shown above the horizontal line, and relatively hydrophilic regions of the protein are below the horizontal line. The cysteine residues (cys) are indicated by short vertical lines just below the hydropathy trace. The dashed vertical line separates the signal sequence (amino acids 1 to 29 of SEQ ID NO:28; SEQ ID NO:30) on the left from the mature protein (amino acids 30 to 370 of SEQ ID NO:28; SEQ ID NO:29) on the right.

The signal peptide prediction program SIGNALP (Nielsen et al., 1997, *Protein Engineering* 10:1-6) predicted that human INTERCEPT 258 includes a 29 amino acid signal peptide (amino acid 1 to amino acid 29 of SEQ ID NO:26; SEQ ID NO:30) preceding the mature INTERCEPT 258 protein (corresponding to amino acid 30 to amino acid 370 of SEQ ID NO:26; SEQ ID NO:29). The molecular weight of human INTERCEPT 258 protein without post-translational modifications is 40.0 kDa prior to the cleavage of the signal peptide, 37.0 kDa after cleavage of the signal peptide.

Human INTERCEPT 258 contains a hydrophobic transmembrane domain at amino acids amino acids 207 to 224 of SEQ ID NO:28 (SEQ ID NO:78) and amino acids 247 to 271 of SEQ ID NO:28 (SEQ ID NO:33). Human INTERCEPT 258 also contains two Ig domains, one at amino acids 49 to 128 of SEQ ID NO:28 (SEQ ID NO:35) and a second at amino acids 167 to 226 of SEQ ID NO:28 (SEQ ID NO:36).

Five N-glycosylation sites are present in human INTERCEPT 258. The first has sequence NLSL and is found at amino acids 108 to 111 of SEQ ID NO:28, the second has the sequence NUTL and is found at amino acids 169 to 172 of SEQ ID NO:28; the third is has the sequence NLSS and is found at amino acids 213 to 216 of SEQ ID NO:28, the fourth has the sequence NUTL and is found at amino acids, 236 to 239 of SEQ ID NO:28, and the fifth has the sequence NGTL and is found at amino acids 307 to 310 of SEQ ID NO:28. Seven protein kinase C phosphorylation sites are present in human INTERCEPT 258. The first has the sequence TSK and is found at amino acids 93 to 95 of SEQ ID NO:28, the second has the sequence SLR and is found at amino acids 110 to 112 of SEQ

ID NO:28, the third has the sequences SIK and is found at amino acids 141 to 143 or SEQ ID NO:28, the fourth has the sequence SCR and is found at amino acids 157 to 159, the fifth has the sequence SPR and is found at amino acids 176 to 179 of SEQ ID NO:28, the sixth has the sequence SAR and is found at amino acids 315 to 317 of SEQ ID NO:28, and the seventh has the sequence SPR and is found at amino acids 344 to 346 of SEQ ID NO:28. The human INTERCEPT 258 protein has seven N-myristoylation sites. The first has the sequence GUTTSK and is found at amino acids 90 to 95 of SEQ ID NO:28, the second has the sequence GANVTL and is found at amino acids 167 to 172 of SEQ ID NO:28, the third has the sequence GVYVCK and is found at amino acids 220 to 225, the fourth has the sequence GTAQCN and is found at amino acids 231 to 236 of SEQ ID NO:28, the fifth has the sequence GTLVGL and is found at amino acids 256 to 261, the sixth has the sequence GLLAGL and is found at amino acids 262 to 267 of SEQ ID NO:28, and the seventh has the sequence GTLSSU and is found at acids 308 to 313 of SEQ ID NO:28.

The human INTERCEPT 258 gene was mapped to human chromosome 11 using Genebridge 4 Human Radiation hybrid mapping panel with GGAGTATCCTTGGTCTACTCC (SEQ ID NO:197) as the forward primer and GAAAGTCTGGAAGGATGGAAGCT (SEQ ID NO:198) as the reverse primer.

Human multi-tissue dot blot analysis of human INTERCEPT 258 expression demonstrates strongest expression in lung, fetal lung, placenta, thyroid gland and mammary gland. Moderate expression is observed in heart, aorta, kidney, small intestine, fetal heart, fetal kidney, fetal spleen, uterus, and stomach. Weak expression is observed in whole brain, amygdala, caudate nucleus, cerebellum, cerebral cortex frontal lobe, hippocampus, medulla oblongata, occipital lobe, putamen, substantia nigra, temporal lobe, thalamus, acumens, spinal cord, skeletal muscle, colon, bladder, prostate, ovary, pancreas, pituitary gland, adrenal gland, salivary gland, liver, spleen, thymus, lymph node, bone marrow, appendix, trachea, fetal brain, fetal liver, and fetal thymus.

A human cancer cell line Northern blot analysis showed a roughly 2.0 kb INTERCEPT 258 band only in the lane containing cell line Chronic Myelogenous Leukemia (K-562). The cancerous cell lines in which INTERCEPT 258 was not expressed include promyeocytic leukemia, Hela, lymphoblastic leukemia, Burkitt's lymphoma Raji, colorectal adenocarcinoma, lung carcinoma and melanoma.

INTERCEPT 258 exhibits homology to a human A33 antigen. A33 antigen is a transmembrane glycoprotein and a member of the immunoglobulin superfamily that may represent a cancer cell marker (Heath et al., 1997, Proc. Natl. Acad. Sci. USA 94:469-474). Figure 23 shows an alignment of the human INTERCEPT 258 amino acid sequence

(SEQ ID NO:28) with the human A33 amino acid sequence (SEQ ID NO:67). The alignment shows that there is a 23.0% overall amino acid sequence identity between human INTERCEPT 258 and A33. Figures 24A-24D show an alignment of the human INTERCEPT 258 nucleotide sequence (SEQ ID NO:26) with that of human A33 nucleotide sequence (SEQ ID NO:68). The alignment shows that there is a 40.6% identity between the two sequences.

Human INTERCEPT 258 nucleotide sequence (SEQ ID NO:26) exhibits homology to human PECAM-1 nucleotide sequence (SEQ ID NO:72). Figures 27A-27E show that there is an overall 40.5% identity between the two nucleotide sequences. Human INTERCEPT 258 amino acid sequence (SEQ ID NO:28) and human PECAM-1 amino acid sequence (SEQ ID NO:73) share less than 18% identity. PECAM-1 (platelet endothelial cell adhesion molecule-1) is an integrin expressed on endothelial cells.

Clone EpT258, which encodes human INTERCEPT 258, was deposited with the American Type Culture Collection (10801 University Boulevard, Manassas, VA 20110-2209) on April 21, 1999 and assigned Accession Number 207222. This deposit will be maintained under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. This deposit was made merely as a convenience for those of skill in the art and is not an admission that a deposit is required under 35 U.S.C. §112.

Mouse INTERCEPT 258

A cDNA encoding mouse INTERCEPT 258 was identified by analyzing the sequences of clones present in a mouse megakaryocyte library for sequences that encode secreted proteins. This analysis led to the identification of a clone, Athmea17c8, encoding full-length mouse INTERCEPT 258. The mouse INTERCEPT 258 cDNA of this clone is 1846 nucleotides long (Figures 20A-20B; SEQ ID NO:37). The open reading frame of this cDNA, nucleotides 107 to 1288 of SEQ ID NO:37 (SEQ ID NO:38), encodes a 394 amino acid transmembrane protein (Figures 20A-20B, SEQ ID NO:39).

Figure 21 depicts a hydropathy plot for mouse INTERCEPT 258. Relatively hydrophobic regions of the protein are above the horizontal line, relatively hydrophilic regions of the protein are below the horizontal line. The cysteine residues (cys) and N-glycosylation sites are (Ngly) are indicated by short vertical lines just below the hydropathy trace. The dashed vertical line separates the signal sequence from the mature protein described below.

The signal peptide prediction program SIGNALP (Nielsen et al., 1997, *Protein Engineering* 10:1-6) predicted that mouse INTERCEPT 258 includes a 29 amino acid

signal peptide (amino acid 1 to amino acid 29 of SEQ ID NO:39; SEQ ID NO:41) preceding the mature INTERCEPT 258 protein (corresponding to amino acid 30 to amino acid 394 of SEQ ID NO:39; SEQ ID NO:40). The molecular weight INTERCEPT 258 without post-translational modifications is 41.8 kDa prior to the cleavage of the signal peptide, 38.90 kDa after cleavage of the signal peptide.

Mouse INTERCEPT 258 contains a hydrophobic transmembrane domain at amino acids 250 to 274 SEQ ID NO:39 (SEQ ID NO:44). Mouse INTERCEPT 258 also contains an Ig domain at amino acids 170 to 229 of SEQ ID NO:39 (SEQ ID NO:71).

Five N-glycosylation sites are present in mouse INTERCEPT 258. The first has sequence NVSL and is found at amino acids 111 to 114 of SEQ ID NO:39, the second has the sequence NVTL and is found at amino acids 172 to 175 of SEQ ID NO:39, the third has the sequence NLSI and is found at amino acids 216 to 219 of SEQ ID NO:39, the fourth has the sequence NVTL and is found at amino acids, 239 to 242 of SEQ ID NO:39, and the fifth has the sequence NGTL and is found at amino acids 310 to 313 of SEQ ID NO:39. Nine protein kinase C phosphorylation sites are present in mouse INTERCEPT 258. the first has the sequence TNK and is found at amino acids 96 to 98 of SEQ ID NO:39, the second has the sequence SSR and is found at amino acids 108 to 110 of SEQ ID NO:39, the third has the sequence SLR and is found at amino acids 113 to 115 of SEQ ID NO:39, the fourth has the sequence TYR and is found at amino acids 126 to 128, the fifth has the sequence SIK and is found at amino acids 144 to 146 of SEQ ID NO:39, the sixth has the sequence SPR and is found at amino acids 179 to 181 of SEQ ID NO:39, the seventh has the sequence SLK and is found at amino acids 211 and 213, the eighth has the sequence SAR and is found at amino acids 318 to 320 of SEQ ID NO:39, and the ninth has the sequence SPR and is found at amino acids 348 to 350 of SEQ ID NO:39. The mouse INTERCEPT 258 contains a casein kinase II phosphorylation site having the sequence TLEE, found at amino acids 280 to 283 of SEQ ID NO:39. The mouse INTERCEPT 258 protein has nine N-myristoylation sites. The first has the sequence GTPETS and is found at amino acids 6 to 11 of SEQ ID NO:39, the second has the sequence GVMTNK and is found at amino acids 125 to 130 of SEQ ID NO:39, the third has the sequence GTYRCS and is found at amino acids 125 to 130, the fourth has the sequence GTNVTL and is found at amino acids 170 to 175 of SEQ ID NO:39, the fifth has the sequence GVYVCK and is found at amino acids 223 to 228, the sixth has the sequence GSKAAV and is found at amino acids 247 to 252, the seventh has the sequence GAVVGT and is found at amino acids 255 to 260 of SEQ ID NO:39, the eighth has sequence GTLSSV and is found at amino acids 311 to 316 of SEQ ID NO:39, and the

ninth has the sequence GGVSSS and is found at amino acids 367 to 372 of SEQ ID NO:39.

An *in situ* expression analysis of INTERCEPT 258 was performed as summarized herein. Mouse INTERCEPT 258 expression during embryogenesis (E73.5 to P1.5 were examined) was observed throughout the animal in a punctate pattern. This pattern is very similar to that seen with the molecule PECAM-1, but at a lower intensity. PECAM-1 is an integrin expressed on endothelial cells. In addition, lung and brown fat exhibited a much higher signal in a more ubiquitous pattern in all embryonic stages examined. Heart and kidney also have a higher expression, but to a lesser degree. Adult mouse INTERCEPT 258 expression was seen in many tissues, often in a multifocal, punctate pattern suggestive of vessels. Expression was also predominant in many highly vascularized tissues such as ovary (especially the septol region), kidney and adrenal cortex.

In general, both embryonic and adult expression patterns were suggestive of endothelial cells being a component in the expression patters observed. In summary, tissues in which INTERCEPT 258 expression was observed were as follows: brain, eye, harderian gland, submanibular gland, bladder, brown fat, stomach, heart, kidney, adrenal gland, colon, liver, thymus, lymph node, spleen, spinal cord, ovary, testes and placenta.

As shown in Figure 22, human INTERCEPT 258 protein and mouse INTERCEPT 258 protein are 62.8% identical.

Mouse INTERCEPT 258 exhibits homology to a human A33 antigen. Figure 25 shows an alignment of mouse INTERCEPT 258 amino acid sequence (SEQ ID NO:39) with the human A33 amino acid sequence (SEQ ID NO:96). The alignment shows that there is a 23% overall amino acid sequence identity between the two sequences. Figures 26A-26D show an alignment of the mouse INTERCEPT 258 nucleotide sequence (SEQ ID NO:37) with that of the human A33 nucleotide sequence (SEQ ID NO:97). The alignment shows that there is a 40% identity between these two nucleotide sequences.

Clone EpTm258, which encodes mouse INTERCEPT 258, was deposited with the American Type Culture Collection (10801 University Boulevard, Manassas, VA 20110-2209) on April 21, 1999 and assigned Accession Number 207221. This deposit will be maintained under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. This deposit was made merely as a convenience for those of skill in the art and is not an admission that a deposit is required under 35 U.S.C. §112.

<u>Uses of INTERCEPT 258 Nucleic acids, Polypeptides, and Modulators Thereof</u>

INTERCEPT 258 was identified as being expressed in a mixed lymphocyte library. In light of this, INTERCEPT 258 nucleic acids, proteins and modulators thereof can be utilized to modulate processes involved in lymphocyte development, differentiation and activity, including, but not limited to development, differentiation and activation of T cells, including T helper, T cytotoxic and non-specific T killer cell types and subtypes, and B cells, immune functions associated with such cells, and amelioration of one or more symptoms associated with abnormal function of such cell types. Such disorders can include, but are not limited to, autoimmune disorders, such as organ specific autoimmune disorders, *e.g.*, autoimmune thyroiditis, Type I diabetes mellitus, insulin-resistant diabetes, autoimmune anemia, multiple sclerosis, and/or systemic autoimmune disorders, *e.g.*, rheumatoid arthritis, lupus or sclerodoma, allergy, including allergic rhinitis and food allergies, asthma, psoriasis, graft rejection, transplantation rejection, graft versus host disease, pathogenic susceptibilities, *e.g.*, susceptibility to certain bacterial or viral pathogens, wound healing and inflammatory reactions.

INTERCEPT 258 includes one or more Ig domains. INTERCEPT 258 nucleic acids, proteins, and modulators thereof can, therefore, be used to modulate immune function, *e.g.*, by the modulation of immunoglobulins and the formation of antibodies. For the same reason, INTERCEPT 258 nucleic acids, proteins, and modulators thereof can be used to modulate immune response, leukocyte trafficking, cancer, Type I immunologic disorders, *e.g.*, anaphylaxis and/or rhinitis, by modulating the interaction between antigens and cell receptors, *e.g.*, high affinity IgE receptors.

INTERCEPT 258 exhibits homology to PECAM-1, a cell adhesion integrin molecule that has been shown to mediate cell-cell interactions, play an important role in bidirectional signal transduction, and may be involved in thrombotic, inflammatory and immunological disorders. As such, INTERCEPT 258 nucleic acids, proteins, and modulators thereof can be utilized to modulate cell/cell interactions and, for example, signal transduction events associated with such interactions. For example, such INTERCEPT 258 compositions and modulators thereof can be used to modulate binding of cellular factors or ECM-associated factors such as integrin and can function to modulate ligand binding to cell surface receptors. Further, such INTERCEPT 258 compositions and modulators thereof can be utilized to ameliorate at least one symptom associated with thrombotic disorders, *e.g.*, stroke, inflammatory processes or disorders, and immune disorders.

In light of INTERCEPT 258 expression, INTERCEPT 258 nucleic acids, proteins and modulators thereof can be utilized modulate development, differentiation, proliferation and/or activity of pulmonary system cells, *e.g.*, lung cell types, and to

modulate a symptom associated with disorders of pulmonary development, differentiation and/or activity, such as lung diseases or disorders associated with abnormal pulmonary development or function, *e.g.*, cystic fibrosis. INTERCEPT 258 nucleic acids, proteins and modulators thereof can also be utilized modulate development, differentiation, proliferation and/or activity of thyroid cells, megakaryocytes or mammary gland cells, and can further be utilized to ameliorate at least one symptom of disorders associated with, abnormal thyroid function, *e.g.*, thyroiditis or Grave's disease, abnormal megakaryocyte differentiation or function, *e.g.*, anemias or leukemias, hematological diseases such as thrombocytopenia, platelet disorders and bleeding disorders, such as hemophilia or abnormal mammary development or function.

INTERCEPT 258 nucleic acids, polypeptides, or modulators thereof can be used to treat renal (kidney) disorders, such as glomerular diseases (*e.g.*, acute and chronic glomerulonephritis, rapidly progressive glomerulonephritis, nephrotic syndrome, focal proliferative glomerulonephritis, glomerular lesions associated with systemic disease, such as systemic lupus erythematosus, Goodpasture's syndrome, multiple myeloma, diabetes, polycystic kidney disease, neoplasia, sickle cell disease, and chronic inflammatory diseases), tubular diseases (*e.g.*, acute tubular necrosis and acute renal failure, polycystic renal diseasemedullary sponge kidney, medullary cystic disease, nephrogenic diabetes, and renal tubular acidosis), tubulointerstitial diseases (*e.g.*, pyelonephritis, drug and toxin induced tubulointerstitial nephritis, hypercalcemic nephropathy, and hypokalemic nephropathy), acute and rapidly progressive renal failure, chronic renal failure, nephrolithiasis, gout, vascular diseases (*e.g.*, hypertension and nephrosclerosis, microangiopathic hemolytic anemia, atheroembolic renal disease, diffuse cortical necrosis, and renal infarcts), or tumors (*e.g.*, renal cell carcinoma and nephroblastoma). INTERCEPT 258 nucleic acids, polypeptides, or modulators thereof can also be used to treat disorders of the brain, such as cerebral edema, hydrocephalus, brain herniations, iatrogenic disease (due to, *e.g.*, infection, toxins, or drugs), inflammations (*e.g.*, bacterial and viral meningitis, encephalitis, and cerebral toxoplasmosis), cerebrovascular diseases (*e.g.*, hypoxia, ischemia, and infarction, intracranial hemorrhage and vascular malformations, and hypertensive encephalopathy), and tumors (*e.g.*, neuroglial tumors, neuronal tumors, tumors of pineal cells, meningeal tumors, primary and secondary lymphomas, intracranial tumors, and medulloblastoma), and to treat injury or trauma to the brain.

INTERCEPT 258 nucleic acids, proteins, and modulators thereof can still further be utilized to modulate development, differentiation proliferation and/or activity of cells involved in kidney or heart formation and function. In addition, such compositions and modulators thereof can be utilized to ameliorate at least one symptom of disorders

associated with abnormal kidney or heart formation or function, including, but not limited to nephritis, coronary disease, atherosclerosis and plaque formation.

INTERCEPT 258 expression indicates that INTERCEPT 258 is involved, in addition to the above, in such processes as thermogenesis, adipocyte function, and vascularization. As such, INTERCEPT 258 nucleic acids, proteins, and modulators thereof can be utilized to modulate such processes as well as for ameliorating at least one symptom associated with such processes. Such disorders include, but are not limited to obesity, regulation of body temperature, and disorders involving abnormal vascularization, *e.g.*, vascularization of solid tumors.

In further light of INTERCEPT 258 expression, as well as in light of its homology to A33 antigen, INTERCEPT 258 nucleic acids, proteins and modulators thereof can be utilized to modulate cell proliferation, including, for example, epithelial, *e.g.*, gastrointestinal tract epithelial cell proliferation, and to ameliorate at least one symptom of cell proliferative disorders such as cancer, and, in particular, chronic myelogenous leukemia, colon cancers, small bowel epithelium cancers and other gastrointestinal tract cancers. Further, INTERCEPT 258 expression can be utilized as a marker for specific tissues (*e.g.*, vascularized tissues) and/or cells (*e.g.*, endothelial cells) in which INTERCEPT 258 is expressed. INTERCEPT 258 nucleic acids can also be utilized for chromosomal mapping.

<u>Human TANGO 281</u>

A cDNA encoding human TANGO 281 was identified by analyzing the sequences of clones present in a human megakarocyte cDNA library. This analysis led to the identification of a clone, AThPb81d10, encoding full-length human TANGO 281. The human TANGO 281 cDNA of this clone is 1812 nucleotides long (Figures 28A-28B; SEQ ID NO:46). The open reading frame of this cDNA, nucleotides 65 to 799 of SEQ ID NO:46 (SEQ ID NO:47), encodes a 245 amino acid transmembrane protein (Figures 28A-28B; SEQ ID NO:48).

The signal peptide prediction program SIGNALP (Nielsen, et al. (1997) *Protein Engineering* 10:1-6) predicted that human TANGO 281 includes an 38 amino acid signal peptide (amino acid 1 to amino acid 38 of SEQ ID NO:48; SEQ ID NO:49) preceding the mature TANGO 281 protein (corresponding to amino acid 39 to amino acid 245 of SEQ ID NO:48; SEQ ID NO:50). The molecular weight of TANGO 281 without post-translational modifications is 26.5 kDa prior to the cleavage of the signal peptide, 20.2 kDa after cleavage of the signal peptide.

Human TANGO 281 is a transmembrane protein which contains one or more of the following domains: (1) an extracellular domain; (2) a transmembrane domain; and (3) a

cytoplasmic domain. The human TANGO 281 protein contains an extracellular domain at amino acids 1 to 123 of SEQ ID NO:48 or a mature extracellular domain at about amino acid residues 39 to 123 of SEQ ID NO:48 (SEQ ID NO:51), a transmembrane domain at amino acid residues 124 to 148 of SEQ ID NO:48 (SEQ ID NO:52), and a cytoplasmic domain at amino acid residues 149 to 245 of SEQ ID NO:48 (SEQ ID NO:53).

Figure 29 depicts a hydropathy plot of human TANGO 281. Relatively hydrophobic regions of the protein are shown above the horizontal line, and relatively hydrophilic regions of the protein are below the horizontal line. The cysteine residues (cys) and potential N-glycosylation sites (Ngly) are indicated by short vertical lines just below the hydropathy trace. The dashed vertical line separates the signal sequence (amino acids 1 to 38 of SEQ ID NO:48; SEQ ID NO:49) on the left from the mature protein (amino acids 38 to 245 of SEQ ID NO:48; SEQ ID NO:50) on the right.

Human TANGO 281 comprises photosystem II 10 kD phosphoprotein (PSBH) domain sequences, which have been shown to be phosphorylated in a light-dependent reaction, from amino acids 41 to 90 and 127 to 182 of SEQ ID NO:48 (SEQ ID NO:54 and SEQ ID NO:55, respectively). Figure 30 depicts an alignment between the PSBH domain (SEQ ID NO:69; Accession No. PF00737) and human TANGO 281 from amino acids 97 to 146 of SEQ ID NO:48. An N-glycosylation site having the sequence NTTT is present in TANGO 281 at about amino acids 160 to 163 of SEQ ID NO:48. Two protein kinase C phosphorylation sites are present in human TANGO 281. The first has the sequence SVR (at amino acids 8 to 10 of SEQ ID NO:48), and the second has the sequence SSR (at amino acids 87 to 89 of SEQ ID NO:48). Three casein kinase II phosphorylation sites are present in human TANGO 281. The first has the sequence SIPE (at amino acids 49 to 52 of SEQ ID NO:48), the second has the sequence SCPD (at amino acids 53 to 56 of SEQ ID NO:48), and the third has the sequence SSLD (at amino acids 108 to 111 of SEQ ID NO:48). Human TANGO 281 has two N-myristylation sites. The first has the sequence GSCSSQ (at amino acids 60 to 65 of SEQ ID NO:48), and the second has the sequence GATVAI (at amino acids 119 to 124 of SEQ ID NO:48).

Nucleic acid base pairs 413 to 746 of human TANGO 281 (SEQ ID NO:46) have 81% identity to the nucleic acid sequence identified as Accession Number AV34245. Nucleic acid base pairs 438 to 746 of human TANGO 281 (SEQ ID NO:46) have 80% identity to a nucleic acid sequence referred to as "gene 31" described in PCT Publication No. WO 98/39446 (SEQ ID NO:70). "Gene 31" is characterized as being expressed primarily in brain and thymus, and to a lesser extent in such organs as liver, skin, bone and bone marrow.

Clone EpT281 was deposited with the American Type Culture Collection (10801 University Boulevard, Manassas, VA 20110-2209) on April 21, 1999 and assigned Accession

Number 207222. This deposit will be maintained under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. This deposit was made merely as a convenience for those of skill in the art and is not an admission that a deposit is required under 35 U.S.C. § 112.

Mouse TANGO 281

A cDNA encoding mouse TANGO 281 was identified in a normal mouse megakaryocyte library by performing expression profiling on megakarocytes obtained from mice with a the deletion of the element of the gata-1 gene responsible for megakaryocyte-specific expression. This analysis led to the identification of a clone, Atmea49d3, encoding full-length mouse TANGO 281. The mouse TANGO 281 cDNA of this clone is 1858 nucleotides long (Figure 30; SEQ ID NO:56). The open reading frame of this cDNA, nucleotides 90 to 728 of SEQ ID NO:56 (SEQ ID NO:57), encodes a 213 amino acid transmembrane protein (Figure 30; SEQ ID NO:58).

The signal peptide prediction program SIGNALP (Nielsen, et al. (1997) *Protein Engineering* 10:1-6) predicted that mouse TANGO 281 includes an 26 amino acid signal peptide (amino acid 1 to amino acid 26 of SEQ ID NO:58; SEQ ID NO:59) preceding the mature TANGO 281 protein (corresponding to amino acid 27 to amino acid 213 of SEQ ID NO:58; SEQ ID NO:60). The molecular weight of mouse TANGO 281 without post-translational modifications is 22.9 kDa prior to the cleavage of the signal peptide, 20.2 kDa after cleavage of the signal peptide.

Mouse TANGO 281 is a transmembrane protein which contains one or more of the following domains: (1) an extracellular domain; (2) a transmembrane domain; and (3) a cytoplasmic domain. The mouse TANGO 281 protein contains an extracellular domain at amino acid residues 27 to 112 of SEQ ID NO:58 (SEQ ID NO:61), a transmembrane domain at amino acid residues 113 to 137 of SEQ ID NO:58 (SEQ ID NO:62), and a cytoplasmic domain at amino acid residues 138 to 213 of SEQ ID NO:58 (SEQ ID NO:63).

Figure 32 depicts a hydropathy plot of mouse TANGO 281. Relatively hydrophobic regions of the protein are shown above the horizontal line, and relatively hydrophilic regions of the protein are below the horizontal line. The cysteine residues (cys) and potential N-glycosylation sites (Ngly) are indicated by short vertical lines just below the hydropathy trace. The dashed vertical line separates the signal sequence (amino acids 1 to 26 of SEQ ID NO:58; SEQ ID NO:59) on the left from the mature protein (amino acids 27 to 213 of SEQ ID NO:58; SEQ ID NO:60) on the right.

Mouse TANGO 281 comprises photosystem II 10 kD phosphoprotein (PSBH) domain sequences, which have been shown to be phosphorylated in a light-dependent reaction, from

amino acids 42 to 91 and 128 to 183 of SEQ ID NO:58 (SEQ ID NO:64 and SEQ ID NO:65, respectively). Two N-glycosylation sites having the sequences NTTT (at amino acids 149 to 152 of SEQ ID NO:58) and NASS (at about amino 189 to 192 of SEQ ID NO:58) are present in TANGO 281. A glycosaminoglycan attachment site having the sequence SGFG is present in mouse TANGO 281, and protein kinase C phosphorylation site having the sequence SSR is present in mouse TANGO 281. Two casein kinase II phosphorylation sites are present in human TANGO 281. The first has the sequence TPAE (at amino acids 80 to 83 of SEQ ID NO:58), and the second has the sequence SSFD (at amino acids 97 to 100 of SEQ ID NO:58). Mouse TANGO 281 has two N-myristylation sites. The first has the sequence GSCSNQ (at amino acids 48 to 53 of SEQ ID NO:58), and the second has the sequence GATVAI (at amino acids 108 to 113 of SEQ ID NO:58).

Northern blot analysis of mouse TANGO 281 expression revealed two mRNA bands, one of approximately 1.8 kb and another approximately 1.4 kb. Expression of the 1.8 kb band was detected in the heart, spleen, lung and kidney, with the greatest abundance detected in the heart and lung, followed by the kidney and trace amounts in the spleen. Expression of the 1.4 kb band was detected in the brain, spleen, and lung. Expression of the 1.4 kb and 1.8 kb species of mouse TANGO 281 was detected in 7 day old normal mouse embryos. Neither the 1.4 kb or the 1.8 kb species of mouse TANGO 281 were detected in 11 day old normal mouse embryos. The 1.8 kb species of mouse TANGO 281 was detected in 15 day old normal mouse embryos at 20 % the level detected in 7 day old normal mouse embryos. Expression of the 1.8 kb species detected in 17 day old normal mouse embryos was comparable to the level of expression detected in 7 day old normal mouse embryos. Expression of mouse TANGO 281 expression was greatly reduced in megakaryocytes obtained from gata-1 knockout mice.

In situ tissue screening was performed on mouse adult and embryonic tissues to analyze for the expression of mouse TANGO 281 mRNA. Mouse TANGO 281 expression was detected predominantly in the adult lymphoid tissues such as the thymus, lymph node, and spleen. In particular, mouse TANGO 281 expression was detected in the following adult tissues: a moderate, ubiquitous signal was detected in the submandibular gland; a strong, ubiquitous signal was detected in the adrenal gland; a strong, multifocal signal was detected in the medulla of the thymus and a moderate, ubiquitous signal was detected in the cortex of the thymus; a strong signal was detected in the lymph node; a strong signal was detected in the follicles of the spleen; a weak signal was detected in the mucosal epithelium of the bladder; a strong signal was detected in the ovaries; a ubiquitous signal was detected in the placenta; a moderate signal was detected in the muscle region of the stomach; a weak signal

in a pattern outlining many of the large airways was detected in lung; a weak, ubiquitous signal was detected in the liver; and a weak, ubiquitous signal was detected in the kidney.

In the case of embryonic expression, mouse TANGO 281 expression was detected in the lung, stomach, thymus and submaxillary gland. In particular, at E16.5 a weak to moderate signal was detected in the intestine and stomach, and a moderate, ubiquitous signal was detected in the lung. At P1.5, a signal was detected in the lung, stomach, thymus, and submaxillary gland.

Figure 33 shows that there is an overall 66.5% identity between the precursor human TANGO 281 amino acid sequence and the precursor mouse TANGO 281 amino acid sequence.

Clone EpT281 was deposited with the American Type Culture Collection (10801 University Boulevard, Manassas, VA 20110-2209) on June 15, 1999 and assigned patent deposit Number PTA-224. This deposit will be maintained under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. This deposit was made merely as a convenience for those of skill in the art and is not an admission that a deposit is required under 35 U.S.C. §112.

Uses of TANGO 281 Nucleic acids, Polypeptides, and Modulators Thereof

As TANGO 281 was originally found in a megakaryocyte library, TANGO 281 nucleic acids, proteins, and modulators thereof can be used to modulate the proliferation, differentiation, and/or function of megakaryocytes and platelets. TANGO 281 nucleic acids, proteins, and modulators thereof can be used to treat associated hematological diseases such as thrombocytopenia, platelet disorders and bleeding disorders (*e.g.*, hemophilia). TANGO 281 nucleic acids, proteins, and modulators thereof can be used to modulate platelet aggregation and degranulation. Further, as TANGO 281 expression varies in mouse embryos during development, TANGO 281 nucleic acids, proteins, and modulators thereof can be used to modulate the development of cells, tissues or organs in embryos.

As TANGO 281 expression is greatly reduced in megakaryocytes obtained from gata-1 knockout mice compared normal mice, TANGO 281 is either a direct or indirect target of gata-1 and has profound biological implications. Gata-1 is a transcription factor involved in the development of hemapoietic cell lineages -- gata-1 expression is required for proper development of erythocytes and megakaryocytes. Although deletion of the gata-1 gene is lethal at the embryonic stage due to a failure to form red blood cells, deletion of only the element of the gata-1 gene responsible for megakaryocyte-specific expression (a 10 kb region of genomic DNA containing a megakaryocyte specific DNase I hypersensitive) is not lethal and results in a reduction in gata-1 expression in the megakaryocyte without affecting gata-1

expression in red blood cells. The megakaryocytes of mice with this element of the gata-1 gene knocked out fail to develop into mature platelets, and the mice experience abnormal bleeding due to their profound thrombocytopenia. TANGO 281 nucleic acids, proteins, and modulators thereof can be used to treat disease and/or disorders associated with gata-1 dysfunction. In light of the reduced expression of TANGO 281 in gata-1 knockout mice, TANGO 281 expression can be utilized as a marker for modulators of gata-1 expression and/or activity.

As TANGO 281 is expressed in the heart, brain, spleen, lung, kidney, embryo and megakaryocytes, TANGO 281 nucleic acids, proteins, and modulators thereof can be used to treat disorders of these cells, tissues, or organs, *e.g.*, ischemic heart disease or atherosclerosis, head trauma, brain cancer, splenic lymphoma, splenomegaly, lung cancer, cystic fibrosis, rheumatoid lung disease, glomerulonephritis, end stage renal disease, uremia, DiGeorge syndrome, thymoma, autoimmune disorders, atresia, Crohns's disease, and various embryonic disorders. TANGO 281 nucleic acids, proteins, and modulators thereof can be used to modulate the bleeding associated with uremia. Further, TANGO 281 nucleic acids, proteins, and modulators thereof can be used to treat hypercoagulation associated with a damaged endothelium, *e.g.*, pre-eclampsia, malignant hypertension, disseminated intravascular coagulopathy, renal transplant rejection, cyclosporin toxicity, microangiopathic hemolytic anemia, and thrombotic thrombocytopenic purpura.

TANGO 281 exhibits homology to a gene referred to as "gene 31" (PCT Publication No. WO98/39446), which is expressed primarily in the brain and thymus. In light of this, TANGO 281 nucleic acids, proteins and modulators thereof can be utilized to ameliorate at least one symptom associated with central nervous (CNS) disorders, hematopoietic disorder, and disorders of the endocrine system.

Further, in light of TANGO 281's pattern of expression in mice, TANGO 281 expression can be utilized as a marker for specific tissues (*e.g.*, lymphoid tissues such as the thymus and spleen) and/or cells (*e.g.*, lymphocytes) in which INTERCEPT 281 is expressed. TANGO 281 nucleic acids can also be utilized for chromosomal mapping.

Tables 1-4 below provide a summary of the sequence information for TANGO 253, TANGO 257, INTERCEPT 258 and TANGO 281.

TABLE 1: Summary of Human TANGO 253, TANGO 257, INTERCEPT 258, and TANGO 281 Sequence Information

Gene	cDNA	ORF	Figure	Accession Number
TANGO 253	SEQ ID NO:1	SEQ ID NO:2	Figure 1	207222
TANGO 257	SEQ ID NO:15	SEQ ID NO:16	Figures 9A-9B	207222

INTERCEPT 258	SEQ ID NO:26	SEQ ID NO:27	Figure17	207222
TANGO 281	SEQ ID NO:46	SEQ ID NO:47	Figures 27	207222

TABLE 2: Summary of Domains of Human TANGO 253, TANGO 257, INTERCEPT 258 and TANGO 281 Proteins

Protein	Signal Sequence	Mature Protein	Extracellular	PSBH	Ig	CIq	Collagen	Transmembrane	Cytoplasmic
TANGO 253	aa 1-15 of SEQ ID NO:3 (SEQ ID NO:5)	aa 16-243 of SEQ ID NO:3 (SEQ ID NO:4)				aa 102-232 of SEQ ID NO:3 (SEQ ID NO:7)	aa 36-45 of SEQ ID NO:3 (SEQ ID NO:6)		
TANGO 257	aa 1-21 of SEQ ID NO:17 (SEQ ID NO:19)	aa 22-406 of SEQ ID NO:17 (SEQ ID NO:18)							
INTERCEPT 258	aa 1-29 of SEQ ID NO:28 (SEQ ID NO:30)	aa 30-370 of SEQ ID NO:28 (SEQ ID NO:29)	aa 30-206 of SEQ ID NO: 28 (SEQ ID NO: 76) aa 272-370 of SEQ ID NO: 28 (SEQ ID NO: 34)		aa 49-128; 167-226 of SEQ ID NO:28 (SEQ ID NO:35; SEQ ID NO:36)			aa 207-224 of SEQ ID NO:28 (SEQ ID NO:78); aa 247-271 of SEQ ID NO: 28 (SEQ ID NO: 33)	aa 225-246 of SEQ ID NO:28 (SEQ ID NO:79)
TANGO 281	aa 1-38 of SEQ ID NO:48 (SEQ ID NO:49)	aa 39-245 of SEQ ID NO:48 (SEQ ID NO:50)	aa 39-123 of SEQ ID NO:48 (SEQ ID NO:51)	aa 41-90; 12-187 of SEQ ID NO:48 (SEQ ID NO:54; SEQ ID NO:55)				aa 124-148 of SEQ ID NO:48 (SEQ ID NO:52)	aa 149-245 of SEQ ID NO:48 (SEQ ID NO:53)

TABLE 3: Summary of Mouse TANGO 253, TANGO 257, INTERCEPT 258 and TANGO 281 Sequence Information

Gene	cDNA	ORF	Figure	Accession Number
TANGO 253	SEQ ID NO:8	SEQ ID NO:9	Figures 3A-3B	207215
TANGO 257	SEQ ID NO:21	SEQ ID NO:22	Figures 11A-11B	207217
INTERCEPT 258	SEQ ID NO:37	SEQ ID NO:38	Figures 20A-20B	207221
TANGO 281	SEQ ID NO:56	SEQ ID NO:57	Figures 31A-31B	PTA-224

TABLE 4: Summary of Domains of Mouse TANGO 253, TANGO 257, INTERCEPT 258 and TANGO 281 Proteins

Protein	Signal Sequence	Mature Protein	Extracellular	PSBH	Ig	CIq	Collagen	Transmembrane	Cytoplasmic
TANGO 253	aa 1-15 of SEQ ID NO:10 (SEQ ID NO:12)	aa 16-243 of SEQ ID NO:10 (SEQ ID NO:11)				aa 105-232 of SEQ ID NO:10 (SEQ ID NO:13)	aa 36-95 of SEQ ID NO:10 (SEQ ID NO:14)		
TANGO 257	aa 1-21 of SEQ ID NO:23 (SEQ ID NO:25)	aa 22-406 of SEQ ID NO:23 (SEQ ID NO:24)							
INTERCEPT 258	aa 1-29 of SEQ ID NO:39 (SEQ ID NO:41)	aa 30-394 of SEQ ID NO:39 (SEQ ID NO:40)	30-249 of SEQ ID NO:39 (SEQ ID NO:83)		aa 170-229 of SEQ ID NO:39 (SEQ ID NO:46)			250 to 274 of SEQ ID NO:39 (SEQ ID NO:44)	275-394 of SEQ ID NO:39 (SEQ ID NO:45)
TANGO 281	aa 1-26 of SEQ ID NO:58 (SEQ ID NO:59)	aa 27-213 of SEQ ID NO:58 (SEQ ID NO:60)	aa 27-112 of SEQ ID NO:58 (SEQ ID NO:61)	aa 42-91; 128-183 of SEQ ID NO:58 (SEQ ID NO:64; SEQ ID NO:65)				aa 113-137 of SEQ ID NO:58 (SEQ ID NO:62)	aa 138-213 of SEQ ID NO:58 (SEQ ID NO:63

Various aspects of the invention are described in further detail in the following subsections:

I. Isolated Nucleic Acid Molecules

One aspect of the invention pertains to isolated nucleic acid molecules that encode a polypeptide of the invention or a biologically active portion thereof, as well as nucleic acid molecules sufficient for use as hybridization probes to identify nucleic acid molecules encoding a polypeptide of the invention and fragments of such nucleic acid molecules suitable for use as PCR primers for the amplification or mutation of nucleic acid molecules. As used herein, the term "nucleic acid molecule" is intended to include DNA molecules (*e.g.*, cDNA or genomic DNA) and RNA molecules (*e.g.*, mRNA) and analogs of the DNA or RNA generated using nucleotide analogs. The nucleic acid molecule can be single-stranded or double-stranded, but preferably is double-stranded DNA. In one embodiment, the nucleic acid molecules of the invention comprise a contiguous open reading frame encoding a polypeptide of the invention.

An "isolated" nucleic acid molecule is one which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid molecule. Preferably, an "isolated" nucleic acid molecule is free of sequences (preferably protein encoding sequences) which naturally flank the nucleic acid (*i.e.*, sequences located at the 5' and 3' ends of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. For example, in various embodiments, the isolated nucleic acid molecule can contain less than about 5 kB, 4 kB, 3 kB, 2 kB, 1 kB, 0.5 kB or 0.1 kB of nucleotide sequences which naturally flank the nucleic acid molecule in genomic DNA of the cell from which the nucleic acid is derived. Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized. As used herein, the term "isolated" when referring to a nucleic acid molecule does not include an isolated chromosome.

A nucleic acid molecule of the present invention, *e.g.*, a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:1, 2, 8, 9, 15, 16, 21, 22, 26, 27, 37, 38, 46, 47, 56, 57, 77, 80, 91, 100, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191 or 192, or a complement thereof, can be isolated using standard molecular biology techniques and the sequence information provided herein. Using all or a portion of the nucleic acid sequences of SEQ ID NO:1, 2,

8, 9, 15, 16, 21, 22, 26, 27, 37, 38, 46, 47, 56, 57, 77, 80, 91, 100, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191 or 192, as a hybridization probe, nucleic acid molecules of the invention can be isolated using standard hybridization and cloning techniques (*e.g.*, as described in Sambrook et al., eds., *Molecular Cloning: A Laboratory Manual, 2nd ed., Cold Spring Harbor Laboratory,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989).

A nucleic acid molecule of the invention can be amplified using cDNA, mRNA or genomic DNA as a template and appropriate oligonucleotide primers according to standard PCR amplification techniques. The nucleic acid so amplified can be cloned into an appropriate vector and characterized by DNA sequence analysis. Furthermore, oligonucleotides corresponding to all or a portion of a nucleic acid molecule of the invention can be prepared by standard synthetic techniques, *e.g.*, using an automated DNA synthesizer.

In another preferred embodiment, an isolated nucleic acid molecule of the invention comprises a nucleic acid molecule which is a complement of the nucleotide sequence of SEQ ID NO:1, 2, 8, 9, 15, 16, 21, 22, 26, 27, 37, 38, 46, 47, 56, 57, 77, 80, 91, 100, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191 or 192, or the nucleotide sequence of the cDNA insert of a clone deposited with the ATCC® as Accession number 207222, Accession Number 207215, Accession number 207217, Accession Number 207221 or patent deposit Number PTA-224, or a portion thereof. A nucleic acid molecule which is complementary to a given nucleotide sequence is one which is sufficiently complementary to the given nucleotide sequence that it can hybridize to the given nucleotide sequence thereby forming a stable duplex.

Moreover, a nucleic acid molecule of the invention can comprise only a portion of a nucleic acid sequence encoding a full length polypeptide of the invention for example, a fragment which can be used as a probe or primer or a fragment encoding a biologically active portion of a polypeptide of the invention. The nucleotide sequence determined from the cloning one gene allows for the generation of probes and primers designed for use in identifying and/or cloning homologues in other cell types, *e.g.*, from other tissues, as well as homologues from other mammals. The probe/primer typically comprises substantially purified oligonucleotide. In one embodiment, the oligonucleotide comprises a region of

nucleotide sequence that hybridizes under stringent conditions to at least about 12, preferably 25, more preferably about 50, 75, 100, 125, 150, 175, 200, 250, 300, 350 or 400 consecutive oligonucleotides of the sense or anti-sense sequence of SEQ ID NO:1, 2, 8, 9, 15, 16, 21, 22, 26, 27, 37, 38, 46, 47, 56, 57, 77, 80, 91, 100, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191 or 192, or the nucleotide sequence of the cDNA insert of a clone deposited with the ATCC® as Accession number 207222, Accession Number 207215, Accession Number 207217, Accession Number 207221, or patent deposit Number PTA-224, or of a naturally occurring mutant of SEQ ID NO:1, 2, 8, 9, 15, 16, 21, 22, 26, 27, 37, 38, 46, 47, 56, 57, 77, 80, 91, 100, 101, 103, 104, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191 or 192. In another embodiment, the oligonucleotide comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least 400, preferably 450, 500, 530, 550, 600, 700, 750, 800, 850, 900, 1000, 1100, 1200 or more consecutive oligonucleotides of the sense of antisense sequence of SED ID NO: 1, 2, 8, 9, 15, 16, 21, 22, 26, 27, 37, 38, 46, 47, 56, 57, 77, 80, 91, 100, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191 or 192 , or the nucleotide sequence of the cDNA insert of a clone deposited with the ATCC® as Accession number 207222, Accession number 207215, Accession number 207217, Accession Number 207221, or patent deposit Number PTA-224, or of a naturally occurring mutant of SEQ ID NO: 1, 2, 8, 9, 15, 16, 21, 22, 26, 27, 37, 38, 46, 47, 56, 57, 77, 80, 91, 100, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191 or 192.

In a preferred embodiment, the oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 450, preferably about 500, 550, 600, 650, 700, 750, 800, 850, 900, 1000, 1100 or 1300 consecutive nucleotides of the sense or anti-sense sequence of SEQ ID NO:1, 103, 105, 107 or 109, or a naturally occurring mutant of SEQ ID NO:1, 103, 105, 107, or 109. In another preferred embodiment, the oligonucleotide typically comprises a region of

nucleotide sequence that hybridizes under stringent conditions to at least about 12, preferably 25, 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700 or 720 consecutive nucleotides of the sense or anti-sense sequence of SEQ ID NO:2, 91, 100, 101 or 80.

In another preferred embodiment, the oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 540, preferably about 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200 or 1250 consecutive nucleotides of the sense or anti-sense sequence of SEQ ID NO:8, 119, 121, 123 or 125, or of a naturally occurring mutant of SEQ ID NO:8, 119, 121, 123 or 125. In another preferred embodiment, the oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 310, preferably about 350, 400, 450, 500, 550, 600, 650 or 700 consecutive nucleotides of the sense or anti-sense sequence of SEQ ID NO:9, 174, 175, 176 or 177, or of a naturally occurring mutant of SEQ ID NO:9, 174, 175, 176 or 177.

In another preferred embodiment, the oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 1800 consecutive nucleotides of the sense or anti-sense sequence of SEQ ID NO:15, 111, 113, 115 or 117, or of a naturally occurring mutant of SEQ ID NO:15, 111, 113, 115 or 117. In another preferred embodiment, the oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 1150 consecutive nucleotides of the sense or anti-sense sequence of SEQ ID NO:16, 170, 171, 172 or 173, or of a naturally occurring mutant of SEQ ID NO:16, 170, 171, 172 or 173.

In another preferred embodiment, the oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 1100, preferably about 1200, 1300, 1400, 1500, 16500 or 1700 consecutive nucleotides of the sense or anti-sense sequence of SEQ ID NO:21, 127, 129, 131 or 133, or of a naturally occurring mutant of SEQ ID NO:21, 127, 129, 131 or 133. In another preferred embodiment, the oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 1150 consecutive nucleotides of the sense or anti-sense sequence of SEQ ID NO:22, 178, 179, 180 or 181, or of a naturally occurring mutant of SEQ ID NO:22, 178, 179, 180 or 181.

In another preferred embodiment, the oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 420, preferably about 450, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700 or 1800 consecutive nucleotides of the sense or anti-sense sequence of SEQ ID

NO:26, 135, 137, 139 or 141, or of a naturally occurring mutant of SEQ ID NO:26, 135, 137, 139 or 141. In another preferred embodiment, the oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12, preferably about 25, more preferably about 50, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700 or 1800 consecutive nucleotides of the sense or anti-sense sequence of SEQ ID NO:27, 182, 183, 184 or 185, or of a naturally occurring mutant of SEQ ID NO:27, 182, 183, 184 or 185.

In another preferred embodiment, the oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 675, preferably about 700, 800, 900, 1000, 1200, 1300, 1400, 1500, 1600, 1700 or 1800 consecutive nucleotides of the sense or anti-sense sequence of SEQ ID NO:37, 143, 145, 147 or 149, or of a naturally occurring mutant of SEQ ID NO:37, 143, 145, 147 or 149. In another preferred embodiment, the oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 500, preferably about 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700 or 1800 consecutive nucleotides of the sense or anti-sense sequence of SEQ ID NO:38, 186, 187, 188 or 189, or of a naturally occurring mutant of SEQ ID NO:38, 186, 187, 188 or 189.

In another preferred embodiment, the oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12, preferably about 25, more preferably about 50, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700 or 1800 consecutive nucleotides of the sense or anti-sense sequence of SEQ ID NO:46, 151, 153, 155 or 157, or of a naturally occurring mutant of SEQ ID NO:46, 151, 153, 155 or 157. In another preferred embodiment, the oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12, preferably about 25, more preferably about 50, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700 or 1800 consecutive nucleotides of the sense or anti-sense sequence of SEQ ID NO:47, 190, 191, 192 or 77, or of a naturally occurring mutant of SEQ ID NO:47, 190, 191, 192 or 77.

In another preferred embodiment, the oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 550, preferably about 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800 or 1850 consecutive nucleotides of the sense or anti-sense sequence of SEQ ID NO:56, 159, 161, 163 or 165, or of a naturally occurring mutant of SEQ ID NO:56, 159, 161, 163 or 165. In another preferred embodiment, the oligonucleotide typically

comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12, preferably about 25, more preferably about 50, 100, 200, 300, 400, 500, 600 or 700 consecutive nucleotides of the sense or anti-sense sequence of SEQ ID NO:57, 166, 167, 168 or 169, or of a naturally occurring mutant of SEQ ID NO:57, 166, 167, 168 or 169.

Probes based on the sequence of a nucleic acid molecule of the invention can be used to detect transcripts or genomic sequences encoding the same protein molecule encoded by a selected nucleic acid molecule. The probe comprises a label group attached thereto, *e.g.*, a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used as part of a diagnostic test kit for identifying cells or tissues which mis-express the protein, such as by measuring levels of a nucleic acid molecule encoding the protein in a sample of cells from a subject, *e.g.*, detecting mRNA levels or determining whether a gene encoding the protein has been mutated or deleted.

A nucleic acid fragment encoding a biologically active portion of a polypeptide of the invention can be prepared by isolating a portion of any of SEQ ID NO:3, 10, 17, 23, 28, 39, 48, 58, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162 or 164 expressing the encoded portion of the polypeptide protein (*e.g.*, by recombinant expression *in vitro*) and assessing the activity of the encoded portion of the polypeptide.

The invention further encompasses nucleic acid molecules that differ from the nucleotide sequence of SEQ ID NO:1, 2, 8, 9, 15, 16, 21, 22, 26, 27, 37, 38, 46, 47, 56, 57, 77, 80, 91, 100, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191 or 192, or the nucleotide sequence of the cDNA insert of a clone deposited with the ATCC® as Accession Number 207222, Accession Number 207215, Accession Number 207217, Accession Number 207221 or patent deposit number PTA-224 due to degeneracy of the genetic code and thus encode the same protein as that encoded by the nucleotide sequence of SEQ ID NO:1, 2, 8, 9, 15, 16, 21, 22, 26, 27, 37, 38, 46, 47, 56, 57, 77, 80, 91, 100, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191or 192, or the nucleotide sequence of the cDNA insert of a clone deposited with the ATCC® as Accession Number 207222, Accession Number 207215, Accession Number 207217, Accession Number 207221 or patent deposit Number PTA-224.

In addition to the nucleotide sequences of SEQ ID NO:1, 2, 8, 9, 15, 16, 21, 22, 26, 27, 37, 38, 46, 47, 56, 57, 77, 80, 91, 100, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191or 192, it will be appreciated by those skilled in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequence may exist within a population (*e.g.*, the human population). Such genetic polymorphisms may exist among individuals within a population due to natural allelic variation.

An allele is one of a group of genes which occur alternatively at a given genetic locus. As used herein, the phrase "allelic variant" refers to a nucleotide sequence which occurs at a given locus or to a polypeptide encoded by the nucleotide sequence. As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules comprising an open reading frame encoding a polypeptide of the invention. Such natural allelic variations can typically result in 1-5% variance in the nucleotide sequence of a given gene. Alternative alleles can be identified by sequencing the gene of interest in a number of different individuals. This can be readily carried out by using hybridization probes to identify the same genetic locus in a variety of individuals. Any and all such nucleotide variations and resulting amino acid polymorphisms or variations that are the result of natural allelic variation and that do not alter the functional activity are intended to be within the scope of the invention.

The human gene for TANGO 253 has been mapped to the long arm of chromosome 11. Flanking markers for this region are D1151356 and D115924. The Jacobsen syndrome (JBS), ED4 (ectodermal dysplasia 4), CMT4B (Charcot Marie Tooth neuropathy), PORC (porphyria, acute) loci also map to this region of the human chromosome. The APOPLP1 (apolipoprotein cluster), DRD2 (dopamine receptor 2), PGL1 (paraganglioma glomus tumors), RDX (radixin), NCAM1 (neural cell adhesion molecule), ARCN1 (archain 1), and IL-10R (IL-10 receptor) genes map to this region of the human chromosome. This region is syntenic to mouse chromosome 9. The ruf (rough fur), lu (luxoid), and atm (ataxia telangiectasia gene mutated in human being) loci also mpa to this region of the mouse chromosome. The ruf (rough fur), lu (luxoi), hmbs (hydroxymethylbilane synthase), IL-10Rα (IL-10 receptor α), and drd2 (dopamine receptor 2) genes also map to this region of the mouse chromosome.

The human gene for TANGO 257 has been mapped to chromosome 1. Flanking markers for ths region are WI-7614 and FB14F9. The WS2B (Waardenburg syndrome) loci also maps to this region of the human chromosome. The NGF-β (nerve growth

factor-β), TSHB (thyroid stimulating hormone), and GSTM1 (glutathione S-transferase cluster) genes also map to this region of the human chromosome. This region is syntenic to mouse chromosome 3. The de (droopy ear) loci maps to this region of the mouse chromosome. The NGF-β (nerve growth factor-β), TSHB (thyroid stimulating hormone), and BCAN (brevican) genes also map to this region of the mouse chromosome.

The human gene for INTERCEPT 258 has been mapped to the long arm of chromosome 11, in the region q23. Flanking markers for this region are D11S936 and D11S933. The CMT4B (Charcot Marie Tooth neuropathy), ED4 (ecotodermal dysplasia), JBS (Jacobsen Syndrome), and TCPT (thrombocytopenia) loci also map to this region of the human chromosome. The APOLP1 (apolipoprotein cluster), DRD2 (dopamine receptor), and RDX (radixin) genes also map to this region of the human chromosome. This region is syntenic to mouse chromosome 9. The atm (ataxia telangiectasia), ruf (rough fur), and vs (variable spotting) loci map to this region of the mouse chromosome. The lu (luxoid), vs (variable spotting), atm (ataxia telangiectasia), rug (rough fur), and lap1 (leucine arylaminopeptidase) genes also map to this region of the mouse chromosome.

Moreover, nucleic acid molecules encoding proteins of the invention from other species (homologues), which have a nucleotide sequence which differs from that of the human or mouse protein described herein are intended to be within the scope of the invention. Nucleic acid molecules corresponding to natural allelic variants and homologues of a cDNA of the invention can be isolated based on their identity to the human nucleic acid molecule disclosed herein using the human cDNAs, or a portion thereof, as a hybridization probe according to standard hybridization techniques under stringent hybridization conditions. For example, a cDNA encoding a soluble form of a membrane-bound protein of the invention isolated based on its hybridization to a nucleic acid molecule encoding all or part of the membrane-bound form. Likewise, a cDNA encoding a membrane-bound form can be isolated based on its hybridization to a nucleic acid molecule encoding all or part of the soluble form.

Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 1000, 1100, 1200 or 1300 contiguous nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence, preferably the coding sequence, of SEQ ID NO:1, 103, 105, 107 or 109, or a complement thereof.

Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700 or

720 contiguous nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence, preferably the coding sequence, of SEQ ID NO:2, 80, 91, 100 or 101, or a complement thereof.

Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 540, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200 or 1250 contiguous nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence, preferably the coding sequence, of SEQ ID NO:8, 119, 121, 123 or 125, or a complement thereof.

Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 310, 350, 400, 450, 500, 550, 600, 650 or 700 contiguous nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence, preferably the coding sequence, of SEQ ID NO:9, 174, 175, 176 or 177, or a complement thereof.

Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 1800 contiguous nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence, preferably the coding sequence, of SEQ ID NO:15, 111, 113, 115 or 117, or a complement thereof.

Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 1150 or 1200 contiguous nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence, preferably the coding sequence, of SEQ ID NO:16, 170, 171, 172 or 173, or a complement thereof.

Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 1100, 1200, 1300, 1400, 1500, 1600 or 1700 contiguous nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence, preferably the coding sequence, of SEQ ID NO:21, 127, 129, 131 or 133, or a complement thereof.

Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 1150 or 1200 contiguous nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence, preferably the coding sequence, of SEQ ID NO:22, 178, 179, 180 or 181, or a complement thereof.

Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 420, 450, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400,

1500, 1600, 1700, or 1800 contiguous nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence, preferably the coding sequence, of SEQ ID No:26, 135, 137, 139 or 141, or a complement thereof.

Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 50, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700 or 1800 contiguous nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence, preferably the coding sequence, of SEQ ID NO:27, 182, 183, 184 or 185, or a complement thereof.

Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 675, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700 or 1800 contiguous nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence, preferably the coding sequence, of SEQ ID NO:37, 143, 145, 147 or 149, or a complement thereof.

Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700 or 1800 contiguous nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence, preferably the coding sequence, of SEQ ID NO:38, 186, 187, 188 or 189, or a complement thereof.

Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 50, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700 or 1800 contiguous nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence, preferably the coding sequence, of SEQ ID NO:46, 151, 153, 155 or 157, or a complement thereof.

Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 50, 100, 200, 300, 400, 500, 600, 700 or 750 contiguous nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence, preferably the coding sequence, of SEQ ID NO:47, 77 190, 191 or 192, or a complement thereof.

Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 550, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800 or 1850 contiguous nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence, preferably the coding sequence, of SEQ ID NO:56, 159, 161, 163 or 165, or a complement thereof.

Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 50, 100, 200, 300, 400, 500, 600 or 700 contiguous nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence, preferably the coding sequence, of SEQ ID NO:57, 166, 167, 168 or 169, or a complement thereof.

As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences at least 60%, 65%, 70%, preferably 75%, identical to each other typically remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. A preferred, non-limiting example of stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45° C, followed by one or more washes in 0.2 X SSC, 0.1% SDS at 50-65° C. Preferably, an isolated nucleic acid molecule of the invention that hybridizes under stringent conditions to the sequence of SEQ ID NO:1, 2, 8, 9, 15, 16, 21, 22, 26, 27, 37, 38, 46, 47, 56, 57, 77, 80, 91, 100, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191 or 192 , or a complement thereof, corresponds to a naturally-occurring nucleic acid molecule. As used herein, a "naturally-occurring" nucleic acid molecule refers to an RNA or DNA molecule having a nucleotide sequence that occurs in nature (*e.g.*, encodes a natural protein).

In addition to naturally-occurring allelic variants of a nucleic acid molecule of the invention sequence that may exist in the population, the skilled artisan will further appreciate that changes can be introduced by mutation thereby leading to changes in the amino acid sequence of the encoded protein, without altering the biological activity of the protein. For example, one can make nucleotide substitutions leading to amino acid substitutions at "non-essential" amino acid residues. A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequence without altering the biological activity, whereas an "essential" amino acid residue is required for biological activity. For example, amino acid residues that are not conserved or only semi-conserved among homologues of various species may be non-essential for activity and thus would be likely targets for alteration. Specific examples of conservative amino acid alterations from the original amino acid sequence of SEQ ID NO:3, 10, 17, 23, 28, 39, 48 or 58 are shown in SEQ ID NO: 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162 or 164.

Alternatively, amino acid residues that are conserved among the homologues of various species (*e.g.*, mouse and human) may be essential for activity and thus would not be likely targets for alteration.

Accordingly, another aspect of the invention pertains to nucleic acid molecules encoding a polypeptide of the invention that contain changes in amino acid residues that are not essential for activity. Such polypeptides differ in amino acid sequence from SEQ ID NO:3, 102, 104, 106 or 108, yet retain biological activity. In one embodiment, the isolated nucleic acid molecule includes a nucleotide sequence encoding a protein that includes an amino acid sequence that is at least about 40%, 45%, 50%, 55%, 60%, 65%, 75%, 85%, 95%, or 98% identical to the amino acid sequence of SEQ ID NO:3, 102, 104, 106 or 108.

Accordingly, another aspect of the invention pertains to nucleic acid molecules encoding a polypeptide of the invention that contain changes in amino acid residues that are not essential for activity. Such polypeptides differ in amino acid sequence from SEQ ID NO:10, 118, 120, 122 or 124 yet retain biological activity. In one embodiment, the isolated nucleic acid molecule includes a nucleotide sequence encoding a protein that includes an amino acid sequence that is at least about 95%, or 98% identical to the amino acid sequence of SEQ ID NO:10, 118, 120, 122 or 124.

Accordingly, another aspect of the invention pertains to nucleic acid molecules encoding a polypeptide of the invention that contain changes in amino acid residues that are not essential for activity. Such polypeptides differ in amino acid sequence from SEQ ID NO:17, 110, 112, 114 or 116 yet retain biological activity. In one embodiment, the isolated nucleic acid molecule includes a nucleotide sequence encoding a protein that includes an amino acid sequence that is at least about 88%, 90%, 95% or 98% identical to the amino acid sequence of SEQ ID NO:17, 110, 112, 114 or 116.

Accordingly, another aspect of the invention pertains to nucleic acid molecules encoding a polypeptide of the invention that contain changes in amino acid residues that are not essential for activity. Such polypeptides differ in amino acid sequence from SEQ ID NO:23, 126, 128, 130 or 132 yet retain biological activity. In one embodiment, the isolated nucleic acid molecule includes a nucleotide sequence encoding a protein that includes an amino acid sequence that is at least about 88%, 90%, 95%, or 98% identical to the amino acid sequence of SEQ ID NO:23, 126, 128, 130 or 132.

Accordingly, another aspect of the invention pertains to nucleic acid molecules encoding a polypeptide of the invention that contain changes in amino acid residues that are not essential for activity. Such polypeptides differ in amino acid sequence from SEQ

ID NO:28, 134, 136, 138, 140, yet retain biological activity. In one embodiment, the isolated nucleic acid molecule includes a nucleotide sequence encoding a protein that includes an amino acid sequence that is at least about 45%, 50%, 55%, 60%, 65%, 75%, 85%, 95%, or 98% identical to the amino acid sequence of SEQ ID NO:28, 134, 136, 138, 140.

Accordingly, another aspect of the invention pertains to nucleic acid molecules encoding a polypeptide of the invention that contain changes in amino acid residues that are not essential for activity. Such polypeptides differ in amino acid sequence from SEQ ID NO:39, 142, 144, 146 or 148, yet retain biological activity. In one embodiment, the isolated nucleic acid molecule includes a nucleotide sequence encoding a protein that includes an amino acid sequence that is at least about 45%, 50%, 55%, 60%, 65%, 75%, 85%, 95%, or 98% identical to the amino acid sequence of SEQ ID NO:39, 142, 144, 146 or 148.

Accordingly, another aspect of the invention pertains to nucleic acid molecules encoding a polypeptide of the invention that contain changes in amino acid residues that are not essential for activity. Such polypeptides differ in amino acid sequence from SEQ ID NO:48, 150, 152, 154, or 156, yet retain biological activity. In one embodiment, the isolated nucleic acid molecule includes a nucleotide sequence encoding a protein that includes an amino acid sequence that is at least about 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 75%, 85%, 95%, or 98% identical to the amino acid sequence of SEQ ID NO:48, 150, 152, 154 or 156.

Accordingly, another aspect of the invention pertains to nucleic acid molecules encoding a polypeptide of the invention that contain changes in amino acid residues that are not essential for activity. Such polypeptides differ in amino acid sequence from SEQ ID NO:58, 158, 160, 162 or 164, yet retain biological activity. In one embodiment, the isolated nucleic acid molecule includes a nucleotide sequence encoding a protein that includes an amino acid sequence that is at least about 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 75%, 85%, 95%, or 98% identical to the amino acid sequence of SEQ ID NO:58, 158, 160, 162 or 164.

An isolated nucleic acid molecule encoding a variant protein can be created by introducing one or more nucleotide substitutions, additions or deletions into the nucleotide sequence of SEQ ID NO:1, 2, 8, 9, 15, 16, 21, 22, 26, 27, 37, 38, 46, 47, 56, 57, 77, 80, 91, 100, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184,

185, 186, 187, 188, 189, 190, 191 or 192 such that one or more amino acid substitutions, additions or deletions are introduced into the encoded protein. Mutations can be introduced by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Alternatively, mutations can be introduced randomly along all or part of the coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for biological activity to identify mutants that retain activity. Following mutagenesis, the encoded protein can be expressed recombinantly and the activity of the protein can be determined.

In a preferred embodiment, a mutant polypeptide that is a variant of a polypeptide of the invention can be assayed for: (1) the ability to form protein: protein interactions with proteins in a signaling pathway of the polypeptide of the invention; (2) the ability to bind a ligand of the polypeptide of the invention; or (3) the ability to bind to an intracellular target protein of the polypeptide of the invention. In yet another preferred embodiment, the mutant polypeptide can be assayed for the ability to modulate cellular proliferation, cellular migration or chemotaxis, or cellular differentiation.

The present invention encompasses antisense nucleic acid molecules, i.e., molecules which are complementary to a sense nucleic acid encoding a polypeptide of the invention, *e.g.*, complementary to the coding strand of a double-stranded cDNA molecule or complementary to an mRNA sequence. Accordingly, an antisense nucleic acid can hydrogen bond to a sense nucleic acid. The antisense nucleic acid can be complementary to an entire coding strand, or to only a portion thereof, *e.g.*, all or part of the protein coding region (or open reading frame). An antisense nucleic acid molecule can be antisense to all or part of a non-coding region of the coding strand of a nucleotide sequence encoding a polypeptide of the invention. The non-coding regions ("5' and 3' untranslated regions") are the 5' and 3' sequences which flank the coding region and are not translated into amino acids.

An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 nucleotides or more in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (*e.g.*, an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, *e.g.*, phosphorothioate derivatives and acridine substituted nucleotides can be used. Examples of modified nucleotides which can be used to generate the antisense nucleic acid include 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an antisense orientation (*i.e.*, RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest, described further in the following subsection).

The antisense nucleic acid molecules of the invention are typically administered to a subject or generated *in situ* such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding a selected polypeptide of the invention to thereby inhibit expression, *e.g.*, by inhibiting transcription and/or translation. The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule which binds to DNA duplexes, through specific interactions in the major groove of the double helix. An example of a route of administration of antisense nucleic acid molecules of the invention includes direct injection at a tissue site. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic

administration, antisense molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell surface, *e.g.*, by linking the antisense nucleic acid molecules to peptides or antibodies which bind to cell surface receptors or antigens. The antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient intracellular concentrations of the antisense molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

An antisense nucleic acid molecule of the invention can be an α-anomeric (alpha) nucleic acid molecule. An α-anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β-units, the strands run parallel to each other (Gaultier et al. (1987) *Nucleic Acids Res.* 15:6625-6641). The antisense nucleic acid molecule can also comprise a 2'-o-methylribonucleotide (Inoue et al. (1987) *Nucleic Acids Res.* 15:6131-6148) or a chimeric RNA-DNA analogue (Inoue et al. (1987) *FEBS Lett.* 215:327-330).

The invention also encompasses ribozymes. Ribozymes are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (*e.g.*, hammerhead ribozymes (described in Haselhoff and Gerlach (1988) *Nature* 334:585-591)) can be used to catalytically cleave mRNA transcripts to thereby inhibit translation of the protein encoded by the mRNA. A ribozyme having specificity for a nucleic acid molecule encoding a polypeptide of the invention can be designed based upon the nucleotide sequence of a cDNA disclosed herein. For example, a derivative of a *Tetrahymena* L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in a Cech et al. U.S. Patent No. 4,987,071; and Cech et al. U.S. Patent No. 5,116,742. Alternatively, an mRNA encoding a polypeptide of the invention can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules. *See, e.g.*, Bartel and Szostak (1993) *Science* 261:1411-1418.

The invention also encompasses nucleic acid molecules which form triple helical structures. For example, expression of a polypeptide of the invention can be inhibited by targeting nucleotide sequences complementary to the regulatory region of the gene encoding the polypeptide (*e.g.*, the promoter and/or enhancer) to form triple helical structures that prevent transcription of the gene in target cells. *See generally* Helene (1991) *Anticancer Drug Des.* 6(6):569-84; Helene (1992) *Ann. N.Y. Acad. Sci.* 660:27-36; and Maher (1992) *Bioassays* 14(12):807-15.

In various embodiments, the nucleic acid molecules of the invention can be modified at the base moiety, sugar moiety or phosphate backbone to improve, *e.g.*, the stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acids can be modified to generate peptide nucleic acids (*see* Hyrup et al. (1996) *Bioorganic & Medicinal Chemistry* 4(1): 5-23). As used herein, the terms "peptide nucleic acids" or "PNAs" refer to nucleic acid mimics, *e.g.*, DNA mimics, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis of PNA oligomers can be performed using standard solid phase peptide synthesis protocols as described in Hyrup et al. (1996), *supra*; Perry-O'Keefe et al. (1996) *Proc. Natl. Acad. Sci. USA* 93: 14670-675.

PNAs can be used in therapeutic and diagnostic applications. For example, PNAs can be used as antisense or antigene agents for sequence-specific modulation of gene expression by, *e.g.*, inducing transcription or translation arrest or inhibiting replication. PNAs can also be used, *e.g.*, in the analysis of single base pair mutations in a gene by, *e.g.*, PNA directed PCR clamping; as artificial restriction enzymes when used in combination with other enzymes, *e.g.*, S1 nucleases (Hyrup (1996), *supra*; or as probes or primers for DNA sequence and hybridization (Hyrup (1996), *supra*; Perry-O'Keefe et al. (1996) *Proc. Natl. Acad. Sci. USA* 93: 14670-675).

In another embodiment, PNAs can be modified, *e.g.*, to enhance their stability or cellular uptake, by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras can be generated which may combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes, *e.g.*, RNAse H and DNA polymerases, to interact with the DNA portion while the PNA portion would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and orientation (Hyrup (1996), *supra*). The synthesis of PNA-DNA chimeras can be performed as described in Hyrup (1996), *supra,* and Finn et al. (1996) *Nucleic Acids Res.* 24(17):3357-63. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry and modified nucleoside analogs. Compounds such as 5'-(4-methoxytrityl)amino-5'-deoxy-thymidine phosphoramidite can be used as a link between the PNA and the 5' end of DNA (Mag et al. (1989) *Nucleic Acids Res.* 17:5973-88). PNA monomers are then coupled in a stepwise manner to produce a

chimeric molecule with a 5' PNA segment and a 3' DNA segment (Finn et al. (1996) *Nucleic Acids Res.* 24(17):3357-63). Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment (Peterser et al. (1975) *Bioorganic Med. Chem. Lett.* 5:1119-11124).

In other embodiments, the oligonucleotide may include other appended groups such as peptides (*e.g.*, for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (*see, e.g.*, Letsinger et al. (1989) *Proc. Natl. Acad. Sci. USA* 86:6553-6556; Lemaitre et al. (1987) *Proc. Natl. Acad. Sci. USA* 84:648-652; PCT Publication No. W0 88/09810) or the blood-brain barrier (*see, e.g.*, PCT Publication No. W0 89/10134). In addition, oligonucleotides can be modified with hybridization-triggered cleavage agents (*see, e.g.*, Krol et al. (1988) *Bio/Techniques* 6:958-976) or intercalating agents (*see, e.g.*, Zon (1988) *Pharm. Res.* 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, *e.g.*, a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

II. Isolated Proteins and Antibodies

One aspect of the invention pertains to isolated proteins, and biologically active portions thereof, as well as polypeptide fragments suitable for use as immunogens to raise antibodies directed against a polypeptide of the invention. In one embodiment, the native polypeptide can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. In another embodiment, polypeptides of the invention are produced by recombinant DNA techniques. Alternative to recombinant expression, a polypeptide of the invention can be synthesized chemically using standard peptide synthesis techniques.

An "isolated" or "purified" protein or biologically active portion thereof is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the protein is derived, or substantially free of chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of protein in which the protein is separated from cellular components of the cells from which it is isolated or recombinantly produced. Thus, protein that is substantially free of cellular material includes preparations of protein having less than about 30%, 20%, 10%, or 5% (by dry weight) of heterologous protein (also referred to herein as a "contaminating protein"). When the protein or biologically active portion thereof is recombinantly produced, it is also preferably substantially free of culture medium, i.e., culture medium represents less than about 20%, 10%, or 5% of the

volume of the protein preparation. When the protein is produced by chemical synthesis, it is preferably substantially free of chemical precursors or other chemicals, i.e., it is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. Accordingly such preparations of the protein have less than about 30%, 20%, 10%, 5% (by dry weight) of chemical precursors or compounds other than the polypeptide of interest.

Biologically active portions of a polypeptide of the invention include polypeptides comprising amino acid sequences sufficiently identical to or derived from the amino acid sequence of the protein (*e.g.*, the amino acid sequence shown in any of SEQ ID NO:4, 6, 7, 13, 14, 18, 23, 28, 33, 34, 35, 36, 39, 42, 44, 45, 48, 51, 52, 53, 54, 55, 58, 61, 62, 63, 64, 65, 71, 76, 34, 78, 79, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 92, 93, 94, 95, 96, 97, 98, or 99 which include fewer amino acids than the full length protein, and exhibit at least one activity of the corresponding full-length protein. Typically, biologically active portions comprise a domain or motif with at least one activity of the corresponding protein. A biologically active portion of a protein of the invention can be a polypeptide which is, for example, 10, 25, 50, 100 or more amino acids in length. Moreover, other biologically active portions, in which other regions of the protein are deleted, can be prepared by recombinant techniques and evaluated for one or more of the functional activities of the native form of a polypeptide of the invention.

Preferred polypeptides have the amino acid sequence of SEQ ID NO:4, 6, 7, 13, 14, 18, 23, 28, 33, 34, 35, 36, 39, 42, 44, 45, 48, 51, 52, 53, 54, 55, 58, 61, 62, 63, 64, 65, 71, 76, 34, 78, 79, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 92, 93, 94, 95, 96, 97, 98, or 99. Other useful proteins are substantially identical (*e.g.*, at least about 45%, preferably 55%, 65%, 75%, 85%, 95%, or 99%) to any of SEQ ID NO:4, 6, 7, 13, 14, 18, 23, 28, 33, 34, 35, 36, 39, 42, 44, 45, 48, 51, 52, 53, 54, 55, 58, 61, 62, 63, 64, 65, 71, 76, 34, 78, 79, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 92, 93, 94, 95, 96, 97, 98, or 99 and retain the functional activity of the protein of the corresponding naturally-occurring protein yet differ in amino acid sequence due to natural allelic variation or mutagenesis.

To determine the percent identity of two amino acid sequences or of two nucleic acids, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is

a function of the number of identical positions shared by the sequences (i.e., % identity = # of identical positions/total # of positions (*e.g.*, overlapping positions) x 100). In one embodiment, the two sequences are the same length.

The determination of percent identity between two sequences can be accomplished using a mathematical algorithm. A preferred, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul (1990) *Proc. Natl. Acad. Sci. USA* 87:2264-2268, modified as in Karlin and Altschul (1993) *Proc. Natl. Acad. Sci. USA* 90:5873-5877. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul, et al. (1990) *J. Mol. Biol.* 215:403-410. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to a protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al. (1997) *Nucleic Acids Res.* 25:3389-3402. Alternatively, PSI-Blast can be used to perform an iterated search which detects distant relationships between molecules (*Id.*). When utilizing BLAST, Gapped BLAST, and PSI-Blast programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used. *See* http://www.ncbi.nlm.nih.gov.

Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, CABIOS (1989). Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the CGC sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. Additional algorithms for sequence analysis are known in the art and include ADVANCE and ADAM as described in Torellis and Robotti (1994) *Comput. Appl. Biosci., 10*:3-5; and FASTA described in Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. 85*:2444-8. Within FASTA, ktup is a control option that sets the sensitivity and speed of the search. If ktup=2, similar regions in the two sequences being compared are found by looking at pairs of aligned residues; if ktup=1, single aligned amino acids are examined. ktup can be set to 2 or 1 for protein sequences, or from 1 to 6 for DNA sequences. The default if ktup is not specified is 2 for proteins and 6 for DNA. For a further description of FASTA parameters, see http://bioweb.pasteur.fr/docs/man/man/fasta.1.html#sect2, the contents of which are incorporated herein by reference.

The percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. In calculating percent identity, only exact matches are counted.

The invention also provides chimeric or fusion proteins. As used herein, a "chimeric protein" or "fusion protein" comprises all or part (preferably biologically active) of a polypeptide of the invention operably linked to a heterologous polypeptide (i.e., a polypeptide other than the same polypeptide of the invention). Within the fusion protein, the term "operably linked" is intended to indicate that the polypeptide of the invention and the heterologous polypeptide are fused in-frame to each other. The heterologous polypeptide can be fused to the N-terminus or C-terminus of the polypeptide of the invention.

One useful fusion protein is a GST fusion protein in which the polypeptide of the invention is fused to the C-terminus of GST sequences. Such fusion proteins can facilitate the purification of a recombinant polypeptide of the invention.

In another embodiment, the fusion protein contains a heterologous signal sequence at its N-terminus. For example, the native signal sequence of a polypeptide of the invention can be removed and replaced with a signal sequence from another protein. For example, the gp67 secretory sequence of the baculovirus envelope protein can be used as a heterologous signal sequence (*Current Protocols in Molecular Biology*, Ausubel et al., eds., John Wiley & Sons, 1992). Other examples of eukaryotic heterologous signal sequences include the secretory sequences of melittin and human placental alkaline phosphatase (Stratagene; La Jolla, California). In yet another example, useful prokaryotic heterologous signal sequences include the phoA secretory signal (Sambrook et al., *supra*) and the protein A secretory signal (Pharmacia Biotech; Piscataway, New Jersey).

In yet another embodiment, the fusion protein is an immunoglobulin fusion protein in which all or part of a polypeptide of the invention is fused to sequences derived from a member of the immunoglobulin protein family. The immunoglobulin fusion proteins of the invention can be incorporated into pharmaceutical compositions and administered to a subject to inhibit an interaction between a ligand (soluble or membrane-bound) and a protein on the surface of a cell (receptor), to thereby suppress signal transduction *in vivo*. The immunoglobulin fusion protein can be used to affect the bioavailability of a cognate ligand of a polypeptide of the invention. Inhibition of ligand/receptor interaction may be useful therapeutically, both for treating proliferative and differentiative disorders and for modulating (*e.g.*, promoting or inhibiting) cell survival. Moreover, the immunoglobulin fusion proteins of the invention can be used as immunogens to produce antibodies directed

against a polypeptide of the invention in a subject, to purify ligands and in screening assays to identify molecules which inhibit the interaction of receptors with ligands.

Chimeric and fusion proteins of the invention can be produced by standard recombinant DNA techniques. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed and reamplified to generate a chimeric gene sequence (*see, e.g.*, Ausubel et al., *supra*). Moreover, many expression vectors are commercially available that already encode a fusion moiety (*e.g.*, a GST polypeptide). A nucleic acid encoding a polypeptide of the invention can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the polypeptide of the invention.

A signal sequence of a polypeptide of the invention (SEQ ID NO:5, 12, 19, 25, 30, 41, 49 or 59) can be used to facilitate secretion and isolation of the secreted protein or other proteins of interest. Signal sequences are typically characterized by a core of hydrophobic amino acids which are generally cleaved from the mature protein during secretion in one or more cleavage events. Such signal peptides contain processing sites that allow cleavage of the signal sequence from the mature proteins as they pass through the secretory pathway. Thus, the invention pertains to the described polypeptides having a signal sequence, as well as to the signal sequence itself and to the polypeptide in the absence of the signal sequence (i.e., the cleavage products). In one embodiment, a nucleic acid sequence encoding a signal sequence of the invention can be operably linked in an expression vector to a protein of interest, such as a protein which is ordinarily not secreted or is otherwise difficult to isolate. The signal sequence directs secretion of the protein, such as from a eukaryotic host into which the expression vector is transformed, and the signal sequence is subsequently or concurrently cleaved. The protein can then be readily purified from the extracellular medium by art recognized methods. Alternatively, the signal sequence can be linked to the protein of interest using a sequence which facilitates purification, such as with a GST domain.

In another embodiment, the signal sequences of the present invention can be used to identify regulatory sequences, *e.g.*, promoters, enhancers, repressors. Since signal sequences are the most amino-terminal sequences of a peptide, it is expected that the nucleic acids which flank the signal sequence on its amino-terminal side will be regulatory sequences which affect transcription. Thus, a nucleotide sequence which encodes all or a portion of a signal sequence can be used as a probe to identify and isolate signal sequences

and their flanking regions, and these flanking regions can be studied to identify regulatory elements therein.

The present invention also pertains to variants of the polypeptides of the invention. Such variants have an altered amino acid sequence which can function as either agonists (mimetics) or as antagonists. Variants can be generated by mutagenesis, *e.g.*, discrete point mutation or truncation. An agonist can retain substantially the same, or a subset, of the biological activities of the naturally occurring form of the protein. An antagonist of a protein can inhibit one or more of the activities of the naturally occurring form of the protein by, for example, competitively binding to a downstream or upstream member of a cellular signaling cascade which includes the protein of interest. Thus, specific biological effects can be elicited by treatment with a variant of limited function. Treatment of a subject with a variant having a subset of the biological activities of the naturally occurring form of the protein can have fewer side effects in a subject relative to treatment with the naturally occurring form of the protein.

Variants of a protein of the invention which function as either agonists (mimetics) or as antagonists can be identified by screening combinatorial libraries of mutants, *e.g.*, truncation mutants, of the protein of the invention for agonist or antagonist activity. In one embodiment, a variegated library of variants is generated by combinatorial mutagenesis at the nucleic acid level and is encoded by a variegated gene library. A variegated library of variants can be produced by, for example, enzymatically ligating a mixture of synthetic oligonucleotides into gene sequences such that a degenerate set of potential protein sequences is expressible as individual polypeptides, or alternatively, as a set of larger fusion proteins (*e.g.*, for phage display). There are a variety of methods which can be used to produce libraries of potential variants of the polypeptides of the invention from a degenerate oligonucleotide sequence. Methods for synthesizing degenerate oligonucleotides are known in the art (*see, e.g.*, Narang (1983) *Tetrahedron* 39:3; Itakura et al. (1984) *Annu. Rev. Biochem.* 53:323; Itakura et al. (1984) *Science* 198:1056; Ike et al. (1983) *Nucleic Acid Res.* 11:477).

In addition, libraries of fragments of the coding sequence of a polypeptide of the invention can be used to generate a variegated population of polypeptides for screening and subsequent selection of variants. For example, a library of coding sequence fragments can be generated by treating a double stranded PCR fragment of the coding sequence of interest with a nuclease under conditions wherein nicking occurs only about once per molecule, denaturing the double stranded DNA, renaturing the DNA to form double stranded DNA which can include sense/antisense pairs from different nicked products, removing single stranded portions from reformed duplexes by treatment with S1 nuclease,

and ligating the resulting fragment library into an expression vector. By this method, an expression library can be derived which encodes N-terminal and internal fragments of various sizes of the protein of interest.

Several techniques are known in the art for screening gene products of combinatorial libraries made by point mutations or truncation, and for screening cDNA libraries for gene products having a selected property. The most widely used techniques, which are amenable to high through-put analysis, for screening large gene libraries typically include cloning the gene library into replicable expression vectors, transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates isolation of the vector encoding the gene whose product was detected. Recursive ensemble mutagenesis (REM), a technique which enhances the frequency of functional mutants in the libraries, can be used in combination with the screening assays to identify variants of a protein of the invention (Arkin and Yourvan (1992) *Proc. Natl. Acad. Sci. USA 89*:7811-7815; Delgrave et al. (1993) *Protein Engineering* 6(3):327-331).

The polypeptides of the invention can exhibit post-translational modifications, including, but not limited to glycosylations, (*e.g.*, N-linked or O-linked glycosylations), myristylations, palmitylations, acetylations and phosphorylations (*e.g.*, serine/threonine or tyrosine). In one embodiment, the TANGO 253, TANGO 257, INTERCEPT 258 or TANGO 281 polypeptides of the invention exhibit reduced levels of O-linked glycosylation and/or N-linked glycosylation relative to endogenously expressed TANGO 253, TANGO 257, INTERCEPT 258 or TANGO 281 polypeptides of the invention do not exhibit O-linked glycosylation or N-linked glycosylation. The post-translational modifications of TANGO 253, TANGO 257, INTERCEPT 258 or TANGO 281 polypeptides will vary depending upon the host cell in which in TANGO 253, TANGO 257, INTERCEPT 258 or TANGO 281 is expressed. Further, post-translational modifications of TANGO 253, TANGO 257, INTERCEPT 258 or TANGO 281 polypeptides such as glycosylation can be prevented by treating cells, *e.g.*, with tunicamycin.

An isolated polypeptide of the invention, or a fragment thereof, can be used as an immunogen to generate antibodies using standard techniques for polyclonal and monoclonal antibody preparation. The full-length polypeptide or protein can be used or, alternatively, the invention provides antigenic peptide fragments for use as immunogens. In one embodiment, an isolated polypeptide or fragment thereof which lacks N– and/or O-linked glycosylation is used as an immunogen to generate antibodies using standard techniques known to those of skill in the art. The antigenic peptide of a protein of the

invention comprises at least 8 (preferably 10, 15, 20, or 30) amino acid residues of the amino acid sequence of SEQ ID NO:3, 10, 17, 23, 28, 39, 48, 58, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162 or 164 and encompasses an epitope of the protein such that an antibody raised against the peptide forms a specific immune complex with the protein.

Preferred epitopes encompassed by the antigenic peptide are regions that are located on the surface of the protein, *e.g.*, hydrophilic regions. Figures 2, 4, 10, 12, 19, 21, 29 and 32, are hydropathy plots of the proteins of the invention. These plots or similar analyses can be used to identify hydrophilic regions.

An immunogen typically is used to prepare antibodies by immunizing a suitable subject, (*e.g.*, rabbit, goat, mouse or other mammal). An appropriate immunogenic preparation can contain, for example, recombinantly expressed or chemically synthesized polypeptide. The preparation can further include an adjuvant, such as Freund's complete or incomplete adjuvant, or similar immunostimulatory agent.

Accordingly, another aspect of the invention pertains to antibodies directed against a polypeptide of the invention. The term "antibody" as used herein refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site which specifically binds an antigen, such as a polypeptide of the invention *e.g.*, an epitope of a polypeptide of the invention. A molecule which specifically binds to a given polypeptide of the invention is a molecule which binds the polypeptide, but does not substantially bind other molecules in a sample, *e.g.*, a biological sample, which naturally contains the polypeptide. Examples of immunologically active portions of immunoglobulin molecules include F(ab) and $F(ab')_2$ fragments which can be generated by treating the antibody with an enzyme such as pepsin. The invention provides polyclonal and monoclonal antibodies. The term "monoclonal antibody" or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope.

Polyclonal antibodies can be prepared as described above by immunizing a suitable subject with a polypeptide of the invention as an immunogen. Preferred polyclonal antibody compositions are ones that have been selected for antibodies directed against a polypeptide or polypeptides of the invention. Particularly preferred polyclonal antibody preparations are ones that contain only antibodies directed against a polypeptide or polypeptides of the invention. Particularly preferred immunogen compositions are

those that contain no other human proteins such as, for example, immunogen compositions made using a non-human host cell for recombinant expression of a polypeptide of the invention. In such a manner, the only human epitope or epitopes recognized by the resulting antibody compositions raised against this immunogen will be present as part of a polypeptide or polypeptides of the invention.

The antibody titer in an immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized polypeptide. If desired, the antibody molecules can be isolated from the mammal (*e.g.*, from the blood) and further purified by well-known techniques, such as protein A chromatography to obtain the IgG fraction. Alternatively, antibodies specific for a protein or polypeptide of the invention can be selected for (*e.g.*, partially purified) or purified by, *e.g.*, affinity chromatography. For example, a recombinantly expressed and purified (or partially purified) protein of the invention is produced as described herein, and covalently or non-covalently coupled to a solid support such as, for example, a chromatography column. The column can then be used to affinity purify antibodies specific for the proteins of the invention from a sample containing antibodies directed against a large number of different epitopes, thereby generating a substantially purified antibody composition, *i.e.*, one that is substantially free of contaminating antibodies. By a substantially purified antibody composition is meant, in this context, that the antibody sample contains at most only 30% (by dry weight) of contaminating antibodies directed against epitopes other than those on the desired protein or polypeptide of the invention, and preferably at most 20%, yet more preferably at most 10%, and most preferably at most 5% (by dry weight) of the sample is contaminating antibodies. A purified antibody composition means that at least 99% of the antibodies in the composition are directed against the desired protein or polypeptide of the invention.

At an appropriate time after immunization, *e.g.*, when the specific antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein (1975) *Nature* 256:495-497, the human B cell hybridoma technique (Kozbor et al. (1983) *Immunol. Today* 4:72), the EBV-hybridoma technique (Cole et al. (1985), *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., pp. 77-96) or trioma techniques. The technology for producing hybridomas is well known (*see generally Current Protocols in Immunology* (1994) Coligan et al. (eds.) John Wiley & Sons, Inc., New York, NY). Hybridoma cells producing a monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants for antibodies that bind the polypeptide of interest, *e.g.*, using a standard ELISA assay.

Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody directed against a polypeptide of the invention can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (*e.g.*, an antibody phage display library) with the polypeptide of interest. Kits for generating and screening phage display libraries are commercially available (*e.g.*, the Pharmacia *Recombinant Phage Antibody System*, Catalog No. 27-9400-01; and the Stratagene *SurfZAP™ Phage Display Kit*, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, U.S. Patent No. 5,223,409; PCT Publication No. WO 92/18619; PCT Publication No. WO 91/17271; PCT Publication No. WO 92/20791; PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT Publication No. WO 92/01047; PCT Publication No. WO 92/09690; PCT Publication No. WO 90/02809; Fuchs et al. (1991) *Bio/Technology* 9:1370-1372; Hay et al. (1992) *Hum. Antibod. Hybridomas* 3:81-85; Huse et al. (1989) *Science* 246:1275-1281; Griffiths et al. (1993) *EMBO J.* 12:725-734.

Additionally, recombinant antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, are within the scope of the invention. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region. (See, *e.g.*, Cabilly et al., U.S. Patent No. 4,816,567; and Boss et al., U.S. Patent No. 4,816397, which are incorporated herein by reference in their entirety.) Humanized antibodies are antibody molecules from non-human species having one or more complementarily determining regions (CDRs) from the non-human species and a framework region from a human immunoglobulin molecule. (See, *e.g.*, Queen, U.S. Patent No. 5,585,089, which is incorporated herein by reference in its entirety.) Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in PCT Publication No. WO 87/02671; European Patent Application 184,187; European Patent Application 171,496; European Patent Application 173,494; PCT Publication No. WO 86/01533; U.S. Patent No. 4,816,567; European Patent Application 125,023; Better et al. (1988) *Science* 240:1041-1043; Liu et al. (1987) *Proc. Natl. Acad. Sci. USA* 84:3439-3443; Liu et al. (1987) *J. Immunol.* 139:3521-3526; Sun et al. (1987) *Proc. Natl. Acad. Sci. USA* 84:214-218; Nishimura et al. (1987) *Canc. Res.* 47:999-1005; Wood et al. (1985) *Nature* 314:446-449; and Shaw et al. (1988) *J. Natl. Cancer Inst.* 80:1553-1559); Morrison (1985) *Science* 229:1202-1207; Oi et al. (1986) *Bio/Techniques* 4:214; U.S.

Patent 5,225,539; Jones et al. (1986) *Nature* 321:552-525; Verhoeyan et al. (1988) *Science* 239:1534; and Beidler et al. (1988) *J. Immunol.* 141:4053-4060.

Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Such antibodies can be produced, for example, using transgenic mice which are incapable of expressing endogenous immunoglobulin heavy and light chains genes, but which can express human heavy and light chain genes. The transgenic mice are immunized in the normal fashion with a selected antigen, *e.g.*, all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar (1995, *Int. Rev. Immunol.* 13:65-93). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, *see, e.g.*, U.S. Patent 5,625,126; U.S. Patent 5,633,425; U.S. Patent 5,569,825; U.S. Patent 5,661,016; and U.S. Patent 5,545,806. In addition, companies such as Abgenix, Inc. (Freemont, CA), can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, *e.g.*, a mouse antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et al. (1994) *Bio/technology* 12:899-903).

An antibody directed against a polypeptide of the invention (*e.g.*, monoclonal antibody) can be used to isolate the polypeptide by standard techniques, such as affinity chromatography or immunoprecipitation. Moreover, such an antibody can be used to detect the protein (*e.g.*, in a cellular lysate or cell supernatant) in order to evaluate the abundance and pattern of expression of the polypeptide. The antibodies can also be used diagnostically to monitor protein levels in tissue as part of a clinical testing procedure, *e.g.*, to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or

acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I, ^{131}I, ^{35}S or ^{3}H.

Further, an antibody (or fragment thereof) can be conjugated to a therapeutic moiety such as a cytotoxin, a therapeutic agent or a radioactive metal ion. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (*e.g.*, methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (*e.g.*, mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.*, dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (*e.g.*, vincristine and vinblastine).

The conjugates of the invention can be used for modifying a given biological response, the drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, d-interferon, β-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophase colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

Techniques for conjugating a therapeutic moiety to antibodies are well known, see, *e.g.*, Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in

Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev., 62:119-58 (1982).

Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980.

Accordingly, in one aspect, the invention provides substantially purified antibodies or fragment thereof, including human, non-human, chimeric, and humanized antibodies, which antibodies or fragments specifically bind to a polypeptide comprising an amino acid sequence of any one of SEQ ID NOs:3, 10, 17, 23, 28, 39, 48, 58, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162 or 164, or an amino acid sequence encoded by the cDNA insert of a clone deposited with the ATCC® as Accession Number 207222, Accession Number 207215, Accession Number 207217, Accession Number 207221, or patent deposit Number PTA-224, or a complement thereof. In another aspect, the invention provides substantially purified antibodies or fragments thereof, including human, non-human, chimeric and humanized antibodies, which antibodies or fragments thereof specifically bind to a polypeptide comprising a fragment of at least 8 contiguous amino acid residues, preferably at least 15 contiguous amino acid residues, of the amino acid sequence of any one of SEQ ID NOs:3, 10, 17, 23, 28, 39, 48, 58, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, or 164.

In another aspect, the invention provides substantially purified antibodies or fragments thereof, including human, non-human, chimeric and humanized antibodies, which antibodies or fragments thereof, which antibodies or fragments thereof specifically bind to a polypeptide comprising an amino acid sequence which is at least 95% identical to the amino acid sequence of any one of SEQ ID NOs:3, 10, 17, 23, 28, 39, 48, 58, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162 or 164, wherein the percent identity is determined using the ALIGN program of the GCG software package with a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4. In another aspect, the invention provides substantially purified antibodies or fragments

thereof, including human, non-human, chimeric and humanized antibodies, which antibodies or fragments thereof specifically bind to a polypeptide comprising and an amino acid sequence which is encoded by a nucleic acid molecule which hybridizes to the nucleic acid molecule consisting of any one of SEQ ID Nos:1, 2, 8, 9, 15, 16, 21, 22, 26, 27, 37, 38, 46, 47, 56, 57, 77, 80, 91, 100, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191or 192, or the cDNA insert of a clone deposited as ATCC® as Accession Number 207222, Accession Number 207215, Accession Number 207217, Accession number 207221 or patent deposit Number PTA-224, or a complement thereof, under conditions of hybridization of 6X SSC at 45°C and washing in 0.2 X SSC, 0.1% SDS at 50°C, 55°C, 60°C or 65°C.

In various embodiments, the substantially purified antibodies or fragments thereof of the invention are polyclonal, monoclonal, Fab fragments, single chain antibodies, or $F(ab')_2$ fragments. The non-human antibodies or fragments thereof of the invention can be goat, mouse, sheep, horse, chicken, rabbit or rat antibodies or antibodies fragments. In a preferred embodiment, the antibodies of the invention are monoclonal antibodies that specifically bind to a polypeptide of the invention.

The substantially purified antibodies or fragments thereof specifically bind to a signal peptide, a secreted sequence, an extracellular domain, a transmembrane or a cytoplasmic domain cytoplasmic membrane of a polypeptide of the invention. In a particularly preferred embodiment, the substantially purified antibodies or fragments thereof of the invention specifically bind to a secreted sequence or an extracellular domain of the amino acid sequence of SEQ ID NO:3, 10, 17, 23, 28, 39, 48, 58, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162 or 164, or the amino acid sequence encoded by the EpT253, EpTm253, EpT257, EpTm257, EpT258, EpTm258, EpT281 or EpTm281 cDNA insert of ATCC® Accession Number 207222, Accession Number 207215, Accession Number 207217, Accession Number 207221, or patent deposit Number PTA-224, or a complement thereof. In one embodiment, the extracellular domain to which the antibody or antibody fragment binds comprises at least 8 contiguous amino acid residues, preferably at least 10 or at least 15 contiguous amino acid residues, of amino acid residues 30 to 206 of SEQ ID NO:28 (SEQ ID NO:76), amino acid residues 272 to 370 of SEQ ID NO:28 (SEQ ID NO:34); amino acid residues 30 to 249 of SEQ ID NO:39 (SEQ ID NO: 83), amino acid residues 39 to 123 of SEQ ID NO:48 (SEQ ID NO:50), or amino acid residues 27 to 112 of SEQ ID NO:58 (SEQ ID NO:61).

Any of the antibodies of the invention can be conjugated to a therapeutic moiety or to a detectable substance. Non-limiting examples of detectable substances that can be conjugated to the antibodies of the invention are an enzyme, a prosthetic group, a fluorescent material, a luminescent material, a bioluminescent material, and a radioactive material.

The invention also provides a kit containing an antibody of the invention conjugated to a detectable substance, and instructions for use. Still another aspect of the invention is a pharmaceutical composition comprising an antibody of the invention and a pharmaceutically acceptable carrier. In preferred embodiments, the pharmaceutical composition contains an antibody of the invention, a therapeutic moiety, and a pharmaceutically acceptable carrier.

Still another aspect of the invention is a method of making an antibody that specifically recognizes TANGO 253, TANGO 257, INTERCEPT 258, and TANGO 281, the method comprising immunizing a mammal with a polypeptide. In one embodiment, the polypeptide used as an immunogens comprises an amino acid sequence of any one of SEQ ID NOs:3, 10, 17, 23, 28, 39, 48, 58, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162 or 164, or an amino acid sequence encoded by the cDNA insert of a clone deposited with the ATCC® as Accession Number 207222, Accession Number 207215, Accession Number 207217, Accession Number 207221, or patent deposit Number PTA-224. In another embodiment, the polypeptide used as an immunogen comprises a fragment of at least 15 amino acid residues, preferably at least 25 amino acid residues, of the amino acid sequence of any one of SEQ ID NOs:3, 10, 17, 23, 28, 39, 48, 58, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162 or 164, or an amino acid sequence which is at least 85%, preferably at least 95% identical to the amino acid sequence of any one of SEQ ID NOs:3, 10, 17, 23, 28, 39, 48, 58, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162 or 164, wherein the percent identity is determined using the ALIGN program of the GCG software package with a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4.

In another embodiment, the polypeptide used as an immunogen comprises an amino acid sequence which is encoded by a nucleic acid molecule which hybridizes to the nucleic acid molecule consisting of any one of SEQ ID NOs:1, 2, 8, 9, 15, 16, 21, 22, 26, 27, 37, 38, 46, 47, 56, 57, 77, 80, 91, 100, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153,

155, 157, 159, 161, 163, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191 or 192, or the cDNA insert of a clone deposited with the ATCC® as Accession Number 207222, Accession Number 207215, Accession Number 207217, Accession Number 207221, or patent deposit Number PTA-224, or a complement thereof, under conditions of hybridization of 6X SSC at 45°C and washing in 0.2 X SSC, 0.1% SDS at 50°C, 55°C, 60°C or 65°C. After immunization, a sample is collected from the mammal that contains an antibody that specifically recognizes TANGO 253, TANGO 257, INTERCEPT 258 or TANGO 281, a fragment thereof, or allellic variant thereof. Preferably, the polypeptide is recombinantly produced using a non-human host cell. Optionally, the antibodies can be further purified from the sample using techniques well known to those of skill in the art. The method can further comprise producing a monoclonal antibody- producing cell from the cells of the mammal. Optionally, antibodies are collected from the antibody-producing cell.

III. Recombinant Expression Vectors and Host Cells

Another aspect of the invention pertains to vectors, preferably expression vectors, containing a nucleic acid encoding a polypeptide of the invention (or a portion thereof). As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors, expression vectors, are capable of directing the expression of genes to which they are operably linked. In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids (vectors). However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The recombinant expression vectors of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell. This means that the recombinant expression vectors include one or more regulatory sequences,

selected on the basis of the host cells to be used for expression, which is operably linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner which allows for expression of the nucleotide sequence (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel, *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, CA (1990). Regulatory sequences include those which direct constitutive expression of a nucleotide sequence in many types of host cell and those which direct expression of the nucleotide sequence only in certain host cells (*e.g.*, tissue-specific regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, etc. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein.

The recombinant expression vectors of the invention can be designed for expression of a polypeptide of the invention in prokaryotic (*e.g.*, *E. coli*) or eukaryotic cells (*e.g.*, insect cells (using baculovirus expression vectors), yeast cells or mammalian cells). Suitable host cells are discussed further in Goeddel, *supra*. Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example using T7 promoter regulatory sequences and T7 polymerase.

Expression of proteins in prokaryotes is most often carried out in *E. coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: 1) to increase expression of recombinant protein; 2) to increase the solubility of the recombinant protein; and 3) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase. Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith and Johnson (1988) *Gene* 67:31-40), pMAL (New England Biolabs, Beverly, MA) and pRIT5

(Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein.

Examples of suitable inducible non-fusion *E. coli* expression vectors include pTrc (Amann et al., (1988) *Gene* 69:301-315) and pET 11d (Studier et al., *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, California (1990) 60-89). Target gene expression from the pTrc vector relies on host RNA polymerase transcription from a hybrid trp-lac fusion promoter. Target gene expression from the pET 11d vector relies on transcription from a T7 gn10-lac fusion promoter mediated by a coexpressed viral RNA polymerase (T7 gn1). This viral polymerase is supplied by host strains BL21(DE3) or HMS174(DE3) from a resident λ prophage harboring a T7 gn1 gene under the transcriptional control of the lacUV 5 promoter.

One strategy to maximize recombinant protein expression in *E. coli* is to express the protein in a host bacteria with an impaired capacity to proteolytically cleave the recombinant protein (Gottesman, *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, California (1990) 119-128). Another strategy is to alter the nucleic acid sequence of the nucleic acid to be inserted into an expression vector so that the individual codons for each amino acid are those preferentially utilized in *E. coli* (Wada et al. (1992) *Nucleic Acids Res.* 20:2111-2118). Such alteration of nucleic acid sequences of the invention can be carried out by standard DNA synthesis techniques.

In another embodiment, the expression vector is a yeast expression vector. Examples of vectors for expression in yeast *S. cerivisae* include pYepSec1 (Baldari et al. (1987) *EMBO J.* 6:229-234), pMFa (Kurjan and Herskowitz, (1982) *Cell* 30:933-943), pJRY88 (Schultz et al. (1987) *Gene* 54:113-123), pYES2 (Invitrogen Corporation, San Diego, CA), and pPicZ (Invitrogen Corp, San Diego, CA).

Alternatively, the expression vector is a baculovirus expression vector. Baculovirus vectors available for expression of proteins in cultured insect cells (*e.g.*, Sf 9 cells) include the pAc series (Smith et al. (1983) *Mol. Cell Biol.* 3:2156-2165) and the pVL series (Lucklow and Summers (1989) *Virology* 170:31-39).

In yet another embodiment, a nucleic acid of the invention is expressed in mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include pCDM8 (Seed (1987) *Nature* 329:840) and pMT2PC (Kaufman et al. (1987) *EMBO J.* 6:187-195). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma, Adenovirus 2,

cytomegalovirus and Simian Virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells see chapters 16 and 17 of Sambrook et al., *supra*.

In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type (*e.g.*, tissue-specific regulatory elements are used to express the nucleic acid). Tissue-specific regulatory elements are known in the art. Non-limiting examples of suitable tissue-specific promoters include the albumin promoter (liver-specific; Pinkert et al. (1987) *Genes Dev.* 1:268-277), lymphoid-specific promoters (Calame and Eaton (1988) *Adv. Immunol.* 43:235-275), in particular promoters of T cell receptors (Winoto and Baltimore (1989) *EMBO J.* 8:729-733) and immunoglobulins (Banerji et al. (1983) *Cell* 33:729-740; Queen and Baltimore (1983) *Cell* 33:741-748), neuron-specific promoters (*e.g.*, the neurofilament promoter; Byrne and Ruddle (1989) *Proc. Natl. Acad. Sci. USA* 86:5473-5477), pancreas-specific promoters (Edlund et al. (1985) *Science* 230:912-916), and mammary gland-specific promoters (*e.g.*, milk whey promoter; U.S. Patent No. 4,873,316 and European Application Publication No. 264,166). Developmentally-regulated promoters are also encompassed, for example the mouse hox promoters (Kessel and Gruss (1990) *Science* 249:374-379) and the beta-fetoprotein promoter (Campes and Tilghman (1989) *Genes Dev.* 3:537-546).

The invention further provides a recombinant expression vector comprising a DNA molecule of the invention cloned into the expression vector in an antisense orientation. That is, the DNA molecule is operably linked to a regulatory sequence in a manner which allows for expression (by transcription of the DNA molecule) of an RNA molecule which is antisense to the mRNA encoding a polypeptide of the invention. Regulatory sequences operably linked to a nucleic acid cloned in the antisense orientation can be chosen which direct the continuous expression of the antisense RNA molecule in a variety of cell types, for instance viral promoters and/or enhancers, or regulatory sequences can be chosen which direct constitutive, tissue specific or cell type specific expression of antisense RNA. The antisense expression vector can be in the form of a recombinant plasmid, phagemid or attenuated virus in which antisense nucleic acids are produced under the control of a high efficiency regulatory region, the activity of which can be determined by the cell type into which the vector is introduced. For a discussion of the regulation of gene expression using antisense genes see Weintraub et al. (*Reviews - Trends in Genetics*, Vol. 1(1) 1986).

Another aspect of the invention pertains to host cells into which a recombinant expression vector of the invention has been introduced. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms

refer not only to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

A host cell can be any prokaryotic (*e.g.*, *E. coli*) or eukaryotic cell (*e.g.*, insect cells, yeast or mammalian cells).

Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, et al. (*supra*), and other laboratory manuals.

For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that encodes a selectable marker (*e.g.*, for resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Preferred selectable markers include those which confer resistance to drugs, such as G418, hygromycin and methotrexate. Cells stably transfected with the introduced nucleic acid can be identified by drug selection (*e.g.*, cells that have incorporated the selectable marker gene will survive, while the other cells die).

In another embodiment, the expression characteristics of an endogenous (*e.g.*, TANGO 253, TANGO 257, INTERCEPT 258 and TANGO 281 genes) within a cell, cell line or microorganism may be modified by inserting a DNA regulatory element heterologous to the endogenous gene of interest into the genome of a cell, stable cell line or cloned microorganism such that the inserted regulatory element is operatively linked with the endogenous gene (*e.g.*, TANGO 253, TANGO 257, INTERCEPT 258 and TANGO 281 genes) and controls, modulates or activates. For example, endogenous TANGO 253, TANGO 257, INTERCEPT 258 and TANGO 281 genes which are normally "transcriptionally silent", *i.e.*, a TANGO 253, TANGO 257, INTERCEPT 258 and TANGO 281 genes which is normally not expressed, or are expressed only at very low levels in a cell line or microorganism, may be activated by inserting a regulatory element which is capable of promoting the expression of a normally expressed gene product in that cell line or microorganism. Alternatively, transcriptionally silent, endogenous TANGO

253, TANGO 257, INTERCEPT 258 and TANGO 281 genes may be activated by insertion of a promiscuous regulatory element that works across cell types.

A heterologous regulatory element may be inserted into a stable cell line or cloned microorganism, such that it is operatively linked with endogenous TANGO 253, TANGO 257, INTERCEPT 258 and TANGO 281 genes, using techniques, such as targeted homologous recombination, which are well known to those of skill in the art, and described *e.g.*, in Chappel, U.S. Patent No. 5,272,071; PCT publication No. WO 91/06667, published May 16, 1991.

A host cell of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce a polypeptide of the invention. Accordingly, the invention further provides methods for producing a polypeptide of the invention using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of invention (into which a recombinant expression vector encoding a polypeptide of the invention has been introduced) in a suitable medium such that the polypeptide is produced. In another embodiment, the method further comprises isolating the polypeptide from the medium or the host cell.

The host cells of the invention can also be used to produce nonhuman transgenic animals. For example, in one embodiment, a host cell of the invention is a fertilized oocyte or an embryonic stem cell into which a sequence encoding a polypeptide of the invention has been introduced. Such host cells can then be used to create non-human transgenic animals in which exogenous sequences encoding a polypeptide of the invention have been introduced into their genome or homologous recombinant animals in which endogenous encoding a polypeptide of the invention sequences have been altered. Such animals are useful for studying the function and/or activity of the polypeptide and for identifying and/or evaluating modulators of polypeptide activity. As used herein, a "transgenic animal" is a non-human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens, amphibians, etc. A transgene is exogenous DNA which is integrated into the genome of a cell from which a transgenic animal develops and which remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, an "homologous recombinant animal" is a non-human animal, preferably a mammal, more preferably a mouse, in which an endogenous gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA

molecule introduced into a cell of the animal, *e.g.*, an embryonic cell of the animal, prior to development of the animal.

A transgenic animal of the invention can be created by introducing nucleic acid encoding a polypeptide of the invention (or a homologue thereof) into the male pronuclei of a fertilized oocyte, *e.g.*, by microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably linked to the transgene to direct expression of the polypeptide of the invention to particular cells. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, U.S. Patent No. 4,873,191 and in Hogan, *Manipulating the Mouse Embryo*, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986) and Wakayama *et al.*, (1999), *Proc. Natl. Acad. Sci. USA*, 96:14984-14989. Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of the transgene in its genome and/or expression of mRNA encoding the transgene in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying the transgene can further be bred to other transgenic animals carrying other transgenes.

To create an homologous recombinant animal, a vector is prepared which contains at least a portion of a gene encoding a polypeptide of the invention into which a deletion, addition or substitution has been introduced to thereby alter, *e.g.*, functionally disrupt, the gene. In a preferred embodiment, the vector is designed such that, upon homologous recombination, the endogenous gene is functionally disrupted (i.e., no longer encodes a functional protein; also referred to as a "knock out" vector). Alternatively, the vector can be designed such that, upon homologous recombination, the endogenous gene is mutated or otherwise altered but still encodes functional protein (*e.g.*, the upstream regulatory region can be altered to thereby alter the expression of the endogenous protein). In the homologous recombination vector, the altered portion of the gene is flanked at its 5' and 3' ends by additional nucleic acid of the gene to allow for homologous recombination to occur between the exogenous gene carried by the vector and an endogenous gene in an embryonic stem cell. The additional flanking nucleic acid sequences are of sufficient length for successful homologous recombination with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5' and 3' ends) are included in the vector (*see, e.g.*, Thomas and Capecchi (1987) *Cell* 51:503 for a description of homologous

recombination vectors). The vector is introduced into an embryonic stem cell line (*e.g.*, by electroporation) and cells in which the introduced gene has homologously recombined with the endogenous gene are selected (*see, e.g.*, Li et al. (1992) *Cell* 69:915). The selected cells are then injected into a blastocyst of an animal (*e.g.*, a mouse) to form aggregation chimeras (*see, e.g.*, Bradley in *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, Robertson, ed. (IRL, Oxford, 1987) pp. 113-152). A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term. Progeny harboring the homologously recombined DNA in their germ cells can be used to breed animals in which all cells of the animal contain the homologously recombined DNA by germline transmission of the transgene. Methods for constructing homologous recombination vectors and homologous recombinant animals are described further in Bradley (1991) *Current Opinion in Bio/Technology* 2:823-829 and in PCT Publication Nos. WO 90/11354, WO 91/01140, WO 92/0968, and WO 93/04169.

In another embodiment, transgenic non-human animals can be produced which contain selected systems which allow for regulated expression of the transgene. One example of such a system is the *cre/loxP* recombinase system of bacteriophage P1. For a description of the *cre/loxP* recombinase system, *see, e.g.*, Lakso et al. (1992) *Proc. Natl. Acad. Sci. USA* 89:6232-6236. Another example of a recombinase system is the FLP recombinase system of *Saccharomyces cerevisiae* (O'Gorman et al. (1991) *Science* 251:1351-1355. If a *cre/loxP* recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the *Cre* recombinase and a selected protein are required. Such animals can be provided through the construction of "double" transgenic animals, *e.g.*, by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase.

Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut et al. (1997) *Nature* 385:810-813 and PCT Publication NOS. WO 97/07668 and WO 97/07669.

IV. Pharmaceutical Compositions

The nucleic acid molecules, polypeptides, and antibodies (also referred to herein as "active compounds") of the invention can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically comprise the nucleic acid molecule, protein, or antibody and a pharmaceutically acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" is intended to include any

and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

The invention includes methods for preparing pharmaceutical compositions for modulating the expression or activity of a polypeptide or nucleic acid of the invention. Such methods comprise formulating a pharmaceutically acceptable carrier with an agent which modulates expression or activity of a polypeptide or nucleic acid of the invention. Such compositions can further include additional active agents. Thus, the invention further includes methods for preparing a pharmaceutical composition by formulating a pharmaceutically acceptable carrier with an agent which modulates expression or activity of a polypeptide or nucleic acid of the invention and one or more additional active compounds.

A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF; Parsippany, NJ) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a

solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound (*e.g.*, a polypeptide or antibody) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed.

Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

For administration by inhalation, the compounds are delivered in the form of an aerosol spray from a pressurized container or dispenser which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

The compounds can also be prepared in the form of suppositories (*e.g.*, with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

For antibodies, the preferred dosage is 0.1 mg/kg to 100 mg/kg of body weight (generally 10 mg/kg to 20 mg/kg). If the antibody is to act in the brain, a dosage of 50 mg/kg to 100 mg/kg is usually appropriate. Generally, partially human antibodies and fully human antibodies have a longer half-life within the human body than other antibodies. Accordingly, lower dosages and less frequent administration is often possible. Modifications such as lipidation can be used to stabilize antibodies and to enhance uptake and tissue penetration (*e.g.*, into the brain). A method for lipidation of antibodies is described by Cruikshank et al. ((1997) *J. Acquired Immune Deficiency Syndromes and Human Retrovirology* 14:193).

As defined herein, a therapeutically effective amount of protein or polypeptide (*i.e.*, an effective dosage) ranges from about 0.001 to 30 mg/kg body weight, preferably about 0.01 to 25 mg/kg body weight, more preferably about 0.1 to 20 mg/kg body weight, and even more preferably about 1 to 10 mg/kg, 2 to 9 mg/kg, 3 to 8 mg/kg, 4 to 7 mg/kg, or 5 to 6 mg/kg body weight.

The skilled artisan will appreciate that certain factors may influence the dosage required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a protein, polypeptide, or antibody can include a single treatment or, preferably, can include a series of treatments. In a preferred example, a subject is treated with antibody, protein, or polypeptide in the range of between about 0.1 to 20 mg/kg body weight, one time per week for between about 1 to 10 weeks, preferably between 2 to 8 weeks, more preferably between about 3 to 7 weeks, and even more preferably for about 4, 5, or 6 weeks. It will also be appreciated that the effective dosage of antibody, protein, or polypeptide used for treatment may increase or decrease over the course of a particular treatment. Changes in dosage may result and become apparent from the results of diagnostic assays as described herein.

The present invention encompasses agents which modulate expression or activity. An agent may, for example, be a small molecule. For example, such small molecules include, but are not limited to, peptides, peptidomimetics, amino acids, amino acid analogs, polynucleotides, polynucleotide analogs, nucleotides, nucleotide analogs, organic or inorganic compounds (*i.e*,. including heteroorganic and organometallic compounds) having a molecular weight less than about 10,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 5,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 1,000 grams per mole,

organic or inorganic compounds having a molecular weight less than about 500 grams per mole, and salts, esters, and other pharmaceutically acceptable forms of such compounds.

It is understood that appropriate doses of small molecule agents depends upon a number of factors within the ken of the ordinarily skilled physician, veterinarian, or researcher. The dose(s) of the small molecule will vary, for example, depending upon the identity, size, and condition of the subject or sample being treated, further depending upon the route by which the composition is to be administered, if applicable, and the effect which the practitioner desires the small molecule to have upon the nucleic acid or polypeptide of the invention. Exemplary doses include milligram or microgram amounts of the small molecule per kilogram of subject or sample weight (*e.g.*, about 1 microgram per kilogram to about 500 milligrams per kilogram, about 100 micrograms per kilogram to about 5 milligrams per kilogram, or about 1 microgram per kilogram to about 50 micrograms per kilogram. It is furthermore understood that appropriate doses of a small molecule depend upon the potency of the small molecule with respect to the expression or activity to be modulated. Such appropriate doses may be determined using the assays described herein. When one or more of these small molecules is to be administered to an animal (*e.g.*, a human) in order to modulate expression or activity of a polypeptide or nucleic acid of the invention, a physician, veterinarian, or researcher may, for example, prescribe a relatively low dose at first, subsequently increasing the dose until an appropriate response is obtained. In addition, it is understood that the specific dose level for any particular animal subject will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, gender, and diet of the subject, the time of administration, the route of administration, the rate of excretion, any drug combination, and the degree of expression or activity to be modulated.

The nucleic acid molecules of the invention can be inserted into vectors and used as gene therapy vectors. Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (U.S. Patent 5,328,470) or by stereotactic injection (*see, e.g.,* Chen et al. (1994) *Proc. Natl. Acad. Sci. USA* 91:3054-3057). The pharmaceutical preparation of the gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, *e.g.*, retroviral vectors, the pharmaceutical preparation can include one or more cells which produce the gene delivery system.

The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

V. Uses and Methods of the Invention

The nucleic acid molecules, proteins, protein homologues, and antibodies described herein can be used in one or more of the following methods: a) screening assays; b) detection assays (*e.g.*, chromosomal mapping, tissue typing, forensic biology); c) predictive medicine (*e.g.*, diagnostic assays, prognostic assays, monitoring clinical trials, and pharmacogenomics); and d) methods of treatment (*e.g.*, therapeutic and prophylactic). The isolated nucleic acid molecules of the invention can be used to express proteins (*e.g.*, via a recombinant expression vector in a host cell in gene therapy applications), to detect mRNA (*e.g.*, in a biological sample) or a genetic lesion, and to modulate activity of a polypeptide of the invention. In addition, the polypeptides of the invention can be used to screen drugs or compounds which modulate activity or expression of a polypeptide of the invention as well as to treat disorders characterized by insufficient or excessive production of a protein of the invention or production of a form of a protein of the invention which has decreased or aberrant activity compared to the wild type protein. In addition, the antibodies of the invention can be used to detect and isolate a protein of the and modulate activity of a protein of the invention.

This invention further pertains to novel agents identified by the above-described screening assays and uses thereof for treatments as described herein.

A. Screening Assays

The invention provides a method (also referred to herein as a "screening assay") for identifying modulators, i.e., candidate or test compounds or agents (*e.g.*, peptides, peptidomimetics, small molecules or other drugs) which bind to polypeptide of the invention or have a stimulatory or inhibitory effect on, for example, expression or activity of a polypeptide of the invention.

In one embodiment, the invention provides assays for screening candidate or test compounds which bind to or modulate the activity of the membrane-bound form of a polypeptide of the invention or biologically active portion thereof. The test compounds of the present invention can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the "one-bead one-compound" library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to peptide libraries, while the other four approaches are applicable to peptide,

non-peptide oligomer or small molecule libraries of compounds (Lam (1997) *Anticancer Drug Des.* 12:145).

Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt et al. (1993) *Proc. Natl. Acad. Sci. USA* 90:6909; Erb et al. (1994) *Proc. Natl. Acad. Sci. USA* 91:11422; Zuckermann et al. (1994). *J. Med. Chem.* 37:2678; Cho et al. (1993) *Science* 261:1303; Carrell et al. (1994) *Angew. Chem. Int. Ed. Engl.* 33:2059; Carell et al. (1994) *Angew. Chem. Int. Ed. Engl.* 33:2061; and Gallop et al. (1994) *J. Med. Chem.* 37:1233.

Libraries of compounds may be presented in solution (*e.g.*, Houghten (1992) *Bio/Techniques* 13:412-421), or on beads (Lam (1991) *Nature* 354:82-84), chips (Fodor (1993) *Nature* 364:555-556), bacteria (U.S. Patent No. 5,223,409), spores (Patent NOS. 5,571,698; 5,403,484; and 5,223,409), plasmids (Cull et al. (1992) *Proc. Natl. Acad. Sci. USA* 89:1865-1869) or phage (Scott and Smith (1990) *Science* 249:386-390; Devlin (1990) *Science* 249:404-406; Cwirla et al. (1990) *Proc. Natl. Acad. Sci. USA* 87:6378-6382; and Felici (1991) *J. Mol. Biol.* 222:301-310).

In one embodiment, an assay is a cell-based assay in which a cell which expresses a membrane-bound form of a polypeptide of the invention, or a biologically active portion thereof, on the cell surface is contacted with a test compound and the ability of the test compound to bind to the polypeptide determined. The cell, for example, can be a yeast cell or a cell of mammalian origin. Determining the ability of the test compound to bind to the polypeptide can be accomplished, for example, by coupling the test compound with a radioisotope or enzymatic label such that binding of the test compound to the polypeptide or biologically active portion thereof can be determined by detecting the labeled compound in a complex. For example, test compounds can be labeled with ^{125}I, ^{35}S, ^{14}C, or ^{3}H, either directly or indirectly, and the radioisotope detected by direct counting of radioemmission or by scintillation counting. Alternatively, test compounds can be enzymatically labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product. In a preferred embodiment, the assay comprises contacting a cell which expresses a membrane-bound form of a polypeptide of the invention, or a biologically active portion thereof, on the cell surface with a known compound which binds the polypeptide to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with the polypeptide, wherein determining the ability of the test compound to interact with the polypeptide comprises determining the ability of the test compound to preferentially

bind to the polypeptide or a biologically active portion thereof as compared to the known compound.

In another embodiment, an assay is a cell-based assay comprising contacting a cell expressing a membrane-bound form of a polypeptide of the invention, or a biologically active portion thereof, on the cell surface with a test compound and determining the ability of the test compound to modulate (*e.g.*, stimulate or inhibit) the activity of the polypeptide or biologically active portion thereof. Determining the ability of the test compound to modulate the activity of the polypeptide or a biologically active portion thereof can be accomplished, for example, by determining the ability of the polypeptide protein to bind to or interact with a target molecule.

Determining the ability of a polypeptide of the invention to bind to or interact with a target molecule can be accomplished by one of the methods described above for determining direct binding. As used herein, a "target molecule" is a molecule with which a selected polypeptide (*e.g.*, a polypeptide of the invention) binds or interacts with in nature, for example, a molecule on the surface of a cell which expresses the selected protein, a molecule on the surface of a second cell, a molecule in the extracellular milieu, a molecule associated with the internal surface of a cell membrane or a cytoplasmic molecule. A target molecule can be a polypeptide of the invention or some other polypeptide or protein. For example, a target molecule can be a component of a signal transduction pathway which facilitates transduction of an extracellular signal (*e.g.*, a signal generated by binding of a compound to a polypeptide of the invention) through the cell membrane and into the cell or a second intercellular protein which has catalytic activity or a protein which facilitates the association of downstream signaling molecules with a polypeptide of the invention. Determining the ability of a polypeptide of the invention to bind to or interact with a target molecule can be accomplished by determining the activity of the target molecule. For example, the activity of the target molecule can be determined by detecting induction of a cellular second messenger of the target (*e.g.*, intracellular Ca^{2+}, diacylglycerol, IP3, etc.), detecting catalytic/enzymatic activity of the target on an appropriate substrate, detecting the induction of a reporter gene (*e.g.*, a regulatory element that is responsive to a polypeptide of the invention operably linked to a nucleic acid encoding a detectable marker, *e.g.*, luciferase), or detecting a cellular response, for example, cellular differentiation, or cell proliferation.

In yet another embodiment, an assay of the present invention is a cell-free assay comprising contacting a polypeptide of the invention or biologically active portion thereof with a test compound and determining the ability of the test compound to bind to the polypeptide or biologically active portion thereof. Binding of the test compound to the

polypeptide can be determined either directly or indirectly as described above. In a preferred embodiment, the assay includes contacting the polypeptide of the invention or biologically active portion thereof with a known compound which binds the polypeptide to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with the polypeptide, wherein determining the ability of the test compound to interact with the polypeptide comprises determining the ability of the test compound to preferentially bind to the polypeptide or biologically active portion thereof as compared to the known compound.

In another embodiment, an assay is a cell-free assay comprising contacting a polypeptide of the invention or biologically active portion thereof with a test compound and determining the ability of the test compound to modulate (*e.g.*, stimulate or inhibit) the activity of the polypeptide or biologically active portion thereof. Determining the ability of the test compound to modulate the activity of the polypeptide can be accomplished, for example, by determining the ability of the polypeptide to bind to a target molecule by one of the methods described above for determining direct binding. In an alternative embodiment, determining the ability of the test compound to modulate the activity of the polypeptide can be accomplished by determining the ability of the polypeptide of the invention to further modulate the target molecule. For example, the catalytic/enzymatic activity of the target molecule on an appropriate substrate can be determined as previously described.

In yet another embodiment, the cell-free assay comprises contacting a polypeptide of the invention or biologically active portion thereof with a known compound which binds the polypeptide to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with the polypeptide, wherein determining the ability of the test compound to interact with the polypeptide comprises determining the ability of the polypeptide to preferentially bind to or modulate the activity of a target molecule.

The cell-free assays of the present invention are amenable to use of both a soluble form or the membrane-bound form of a polypeptide of the invention. In the case of cell-free assays comprising the membrane-bound form of the polypeptide, it may be desirable to utilize a solubilizing agent such that the membrane-bound form of the polypeptide is maintained in solution. Examples of such solubilizing agents include non-ionic detergents such as n-octylglucoside, n-dodecylglucoside, n-octylmaltoside, octanoyl-N-methylglucamide, decanoyl-N-methylglucamide, Triton X-100, Triton X-114, Thesit, Isotridecypoly(ethylene glycol ether)n, 3-[(3-cholamidopropyl)dimethylamminio]-1-propane sulfonate (CHAPS),

3-[(3-cholamidopropyl)dimethylamminio]-2-hydroxy-1-propane sulfonate (CHAPSO), or N-dodecyl=N,N-dimethyl-3-ammonio-1-propane sulfonate.

In more than one embodiment of the above assay methods of the present invention, it may be desirable to immobilize either the polypeptide of the invention or its target molecule to facilitate separation of complexed from uncomplexed forms of one or both of the proteins, as well as to accommodate automation of the assay. Binding of a test compound to the polypeptide, or interaction of the polypeptide with a target molecule in the presence and absence of a candidate compound, can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtitre plates, test tubes, and micro-centrifuge tubes. In one embodiment, a fusion protein can be provided which adds a domain that allows one or both of the proteins to be bound to a matrix. For example, glutathione-S-transferase fusion proteins or glutathione-S-transferase fusion proteins can be adsorbed onto glutathione sepharose beads (Sigma Chemical; St. Louis, MO) or glutathione derivatized microtitre plates, which are then combined with the test compound or the test compound and either the non-adsorbed target protein or A polypeptide of the invention, and the mixture incubated under conditions conducive to complex formation (*e.g.*, at physiological conditions for salt and pH). Following incubation, the beads or microtitre plate wells are washed to remove any unbound components and complex formation is measured either directly or indirectly, for example, as described above. Alternatively, the complexes can be dissociated from the matrix, and the level of binding or activity of the polypeptide of the invention can be determined using standard techniques.

Other techniques for immobilizing proteins on matrices can also be used in the screening assays of the invention. For example, either the polypeptide of the invention or its target molecule can be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated polypeptide of the invention or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques well known in the art (*e.g.*, biotinylation kit, Pierce Chemicals; Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). Alternatively, antibodies reactive with the polypeptide of the invention or target molecules but which do not interfere with binding of the polypeptide of the invention to its target molecule can be derivatized to the wells of the plate, and unbound target or polypeptide of the invention trapped in the wells by antibody conjugation. Methods for detecting such complexes, in addition to those described above for the GST-immobilized complexes, include immunodetection of complexes using antibodies reactive with the polypeptide of the invention or target

molecule, as well as enzyme-linked assays which rely on detecting an enzymatic activity associated with the polypeptide of the invention or target molecule.

In another embodiment, modulators of expression of a polypeptide of the invention are identified in a method in which a cell is contacted with a candidate compound and the expression of the selected mRNA or protein (i.e., the mRNA or protein corresponding to a polypeptide or nucleic acid of the invention) in the cell is determined. The level of expression of the selected mRNA or protein in the presence of the candidate compound is compared to the level of expression of the selected mRNA or protein in the absence of the candidate compound. The candidate compound can then be identified as a modulator of expression of the polypeptide of the invention based on this comparison. For example, when expression of the selected mRNA or protein is greater (statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of the selected mRNA or protein expression. Alternatively, when expression of the selected mRNA or protein is less (statistically significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of the selected mRNA or protein expression. The level of the selected mRNA or protein expression in the cells can be determined by methods described herein.

In yet another aspect of the invention, a polypeptide of the inventions can be used as "bait proteins" in a two-hybrid assay or three hybrid assay (*see, e.g.*, U.S. Patent No. 5,283,317; Zervos et al. (1993) *Cell* 72:223-232; Madura et al. (1993) *J. Biol. Chem.* 268:12046-12054; Bartel et al. (1993) *Bio/Techniques* 14:920-924; Iwabuchi et al. (1993) *Oncogene* 8:1693-1696; and PCT Publication No. WO 94/10300), to identify other proteins, which bind to or interact with the polypeptide of the invention and modulate activity of the polypeptide of the invention. Such binding proteins are also likely to be involved in the propagation of signals by the polypeptide of the inventions as, for example, upstream or downstream elements of a signaling pathway involving the polypeptide of the invention.

This invention further pertains to novel agents identified by the above-described screening assays and uses thereof for treatments as described herein.

B. Detection Assays

Portions or fragments of the cDNA sequences identified herein (and the corresponding complete gene sequences) can be used in numerous ways as polynucleotide reagents. For example, these sequences can be used to: (i) map their respective genes on a

chromosome and, thus, locate gene regions associated with genetic disease; (ii) identify an individual from a minute biological sample (tissue typing); and (iii) aid in forensic identification of a biological sample. These applications are described in the subsections below.

1. Chromosome Mapping

Once the sequence (or a portion of the sequence) of a gene has been isolated, this sequence can be used to map the location of the gene on a chromosome. Accordingly, nucleic acid molecules described herein or fragments thereof, can be used to map the location of the corresponding genes on a chromosome. The mapping of the sequences to chromosomes is an important first step in correlating these sequences with genes associated with disease.

Briefly, genes can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp in length) from the sequence of a gene of the invention. Computer analysis of the sequence of a gene of the invention can be used to rapidly select primers that do not span more than one exon in the genomic DNA, thus complicating the amplification process. These primers can then be used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the gene sequences will yield an amplified fragment. For a review of this technique, see D'Eustachio et al. ((1983) *Science* 220:919-924).

PCR mapping of somatic cell hybrids is a rapid procedure for assigning a particular sequence to a particular chromosome. Three or more sequences can be assigned per day using a single thermal cycler. Using the nucleic acid sequences of the invention to design oligonucleotide primers, sublocalization can be achieved with panels of fragments from specific chromosomes. Other mapping strategies which can similarly be used to map a gene to its chromosome include *in situ* hybridization (described in Fan et al. (1990) *Proc. Natl. Acad. Sci. USA* 87:6223-27), pre-screening with labeled flow-sorted chromosomes (CITE), and pre-selection by hybridization to chromosome specific cDNA libraries. Fluorescence *in situ* hybridization (FISH) of a DNA sequence to a metaphase chromosomal spread can further be used to provide a precise chromosomal location in one step. For a review of this technique, see Verma et al., (Human Chromosomes: A Manual of Basic Techniques (Pergamon Press, New York, 1988)).

Reagents for chromosome mapping can be used individually to mark a single chromosome or a single site on that chromosome, or panels of reagents can be used for marking multiple sites and/or multiple chromosomes. Reagents corresponding to

noncoding regions of the genes actually are preferred for mapping purposes. Coding sequences are more likely to be conserved within gene families, thus increasing the chance of cross hybridizations during chromosomal mapping.

Once a sequence has been mapped to a precise chromosomal location, the physical position of the sequence on the chromosome can be correlated with genetic map data. (Such data are found, for example, in V. McKusick, Mendelian Inheritance in Man, available on-line through Johns Hopkins University Welch Medical Library). The relationship between genes and disease, mapped to the same chromosomal region, can then be identified through linkage analysis (co-inheritance of physically adjacent genes), described in, *e.g.*, Egeland et al. (1987) *Nature* 325:783-787.

Moreover, differences in the DNA sequences between individuals affected and unaffected with a disease associated with a gene of the invention can be determined. If a mutation is observed in some or all of the affected individuals but not in any unaffected individuals, then the mutation is likely to be the causative agent of the particular disease. Comparison of affected and unaffected individuals generally involves first looking for structural alterations in the chromosomes such as deletions or translocations that are visible from chromosome spreads or detectable using PCR based on that DNA sequence. Ultimately, complete sequencing of genes from several individuals can be performed to confirm the presence of a mutation and to distinguish mutations from polymorphisms.

Furthermore, the nucleic acid sequences disclosed herein can be used to perform searches against "mapping databases", *e.g.*, BLAST-type search, such that the chromosome position of the gene is identified by sequence homology or identity with known sequence fragments which have been mapped to chromosomes.

In the instant case, the human gene for INTERCEPT 258 has been mapped to the long arm of chromosome 11, in the region q23. Flanking markers for this region are D11S936 and D11S933. The CMT4B (Charcot Marie Tooth neuropathy), ED4 (ecotodermal dysplasia), JBS (Jacobsen Syndrome), TCPT (thrombocytopenia) loci also map to this region of the human chromosome. The APOLP1 (apoplipoprotein cluster), DRD2 (dopamine receptor), and RDX (radixin) genes also map to this region of the human chromosome. This region is syntenic to mouse chromosome 9. The atm (ataxia telangiectasia), ruf (rough fur), and vs (variable spotting) loci map to this region of the mouse chromosome. The lu (luxoid), vs (variable spotting), atm (ataxia telangiectasia), rug (rough fur), and lap1 (leucine arylaminopeptidase) genes also map to this region of the mouse chromosome.

A polypeptide and fragments and sequences thereof and antibodies specific thereto can be used to map the location of the gene encoding the polypeptide on a chromosome. This mapping can be carried out by specifically detecting the presence of the polypeptide in members of a panel of somatic cell hybrids between cells of a first species of animal from which the protein originates and cells from a second species of animal and then determining which somatic cell hybrid(s) expresses the polypeptide and noting the chromosome(s) from the first species of animal that it contains. For examples of this technique, see Pajunen *et al.* (1988) *Cytogenet. Cell Genet.* *47*:37-41 and Van Keuren *et al.* (1986) *Hum. Genet.* *74*:34-40. Alternatively, the presence of the polypeptide in the somatic cell hybrids can be determined by assaying an activity or property of the polypeptide, for example, enzymatic activity, as described in Bordelon-Riser *et al.* (1979) *Somatic Cell Genetics* *5*:597-613 and Owerbach *et al.* (1978) *Proc. Natl. Acad. Sci. USA* *75*:5640-5644.

2. Tissue Typing

The nucleic acid sequences of the present invention can also be used to identify individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identification. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The sequences of the present invention are useful as additional DNA markers for RFLP (described in U.S. Patent 5,272,057).

Furthermore, the sequences of the present invention can be used to provide an alternative technique which determines the actual base-by-base DNA sequence of selected portions of an individual's genome. Thus, the nucleic acid sequences described herein can be used to prepare two PCR primers from the 5' and 3' ends of the sequences. These primers can then be used to amplify an individual's DNA and subsequently sequence it.

Panels of corresponding DNA sequences from individuals, prepared in this manner, can provide unique individual identifications, as each individual will have a unique set of such DNA sequences due to allelic differences. The sequences of the present invention can be used to obtain such identification sequences from individuals and from tissue. The nucleic acid sequences of the invention uniquely represent portions of the human genome. Allelic variation occurs to some degree in the coding regions of these

sequences, and to a greater degree in the noncoding regions. It is estimated that allelic variation between individual humans occurs with a frequency at about once per each 500 bases. Each of the sequences described herein can, to some degree, be used as a standard against which DNA from an individual can be compared for identification purposes. Because greater numbers of polymorphisms occur in the noncoding regions, fewer sequences are necessary to differentiate individuals. The noncoding sequences of SEQ ID NO:1, 8, 15, 21, 26, 37, 46 or 56, can comfortably provide positive individual identification with a panel of perhaps 10 to 1,000 primers which each yield a noncoding amplified sequence of 100 bases. If predicted coding sequences, such as those in SEQ ID NO:2, 9, 16, 22, 27, 38, 47 or 57 are used, a more appropriate number of primers for positive individual identification would be 500-2,000.

If a panel of reagents from the nucleic acid sequences described herein is used to generate a unique identification database for an individual, those same reagents can later be used to identify tissue from that individual. Using the unique identification database, positive identification of the individual, living or dead, can be made from extremely small tissue samples.

3. Use of Partial Gene Sequences in Forensic Biology

DNA-based identification techniques can also be used in forensic biology. Forensic biology is a scientific field employing genetic typing of biological evidence found at a crime scene as a means for positively identifying, for example, a perpetrator of a crime. To make such an identification, PCR technology can be used to amplify DNA sequences taken from very small biological samples such as tissues, *e.g.*, hair or skin, or body fluids, *e.g.*, blood, saliva, or semen found at a crime scene. The amplified sequence can then be compared to a standard, thereby allowing identification of the origin of the biological sample.

The sequences of the present invention can be used to provide polynucleotide reagents, *e.g.*, PCR primers, targeted to specific loci in the human genome, which can enhance the reliability of DNA-based forensic identifications by, for example, providing another "identification marker" (i.e. another DNA sequence that is unique to a particular individual). As mentioned above, actual base sequence information can be used for identification as an accurate alternative to patterns formed by restriction enzyme generated fragments. Sequences targeted to noncoding regions are particularly appropriate for this use as greater numbers of polymorphisms occur in the noncoding regions, making it easier to differentiate individuals using this technique. Examples of polynucleotide reagents

include the nucleic acid sequences of the invention or portions thereof, *e.g.*, fragments derived from noncoding regions having a length of at least 20 or 30 bases.

The nucleic acid sequences described herein can further be used to provide polynucleotide reagents, *e.g.*, labeled or labelable probes which can be used in, for example, an *in situ* hybridization technique, to identify a specific tissue, *e.g.*, brain tissue. This can be very useful in cases where a forensic pathologist is presented with a tissue of unknown origin. Panels of such probes can be used to identify tissue by species and/or by organ type.

C. Predictive Medicine

The present invention also pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, and monitoring clinical trials are used for prognostic (predictive) purposes to thereby treat an individual prophylactically. Accordingly, one aspect of the present invention relates to diagnostic assays for determining TANGO 253, TANGO 257, INTERCEPT 258, or TANGO 281 protein and/or nucleic acid expression as well as TANGO 253, TANGO 257, INTERCEPT 258, or TANGO 281 activity, in the context of a biological sample (*e.g.*, blood, serum, cells, tissue) to thereby determine whether an individual is afflicted with a disease or disorder, or is at risk of developing a disorder, associated with aberrant or unwanted TANGO 253, TANGO 257, INTERCEPT 258, or TANGO 281 expression or activity. The invention also provides for prognostic (or predictive) assays for determining whether an individual is at risk of developing a disorder associated with TANGO 253, TANGO 257, INTERCEPT 258, or TANGO 281 protein, nucleic acid expression or activity. For example, mutations in a TANGO 253, TANGO 257, INTERCEPT 258, or TANGO 281 gene can be assayed in a biological sample. Such assays can be used for prognostic or predictive purpose to thereby prophylactically treat an individual prior to the onset of a disorder characterized by or associated with TANGO 253, TANGO 257, INTERCEPT 258, or TANGO 281 protein, nucleic acid expression or activity.

As an alternative to making determinations based on the absolute expression level of selected genes, determinations may be based on the normalized expression levels of these genes. Expression levels are normalized by correcting the absolute expression level of a TANGO 253, TANGO 257, INTERCEPT 258, or TANGO 281 gene by comparing its expression to the expression of a gene that is not a TANGO 253, TANGO 257, INTERCEPT 258, or TANGO 281 gene, *e.g.*, a housekeeping gene that is constitutively expressed. Suitable genes for normalization include housekeeping genes such as the actin

gene. This normalization allows the comparison of the expression level in one sample, *e.g.*, a patient sample, to another sample, *e.g.*, a sample from an individual without a particular disease or disorder, or a sample from a healthy individual, or between samples from different sources.

Alternatively, the expression level can be provided as a relative expression level. To determine a relative expression level of a gene, the level of expression of the gene is determined for 10 or more samples of different cell isolates (*e.g.*, neural cell isolates, glial cell isolates, immune cell isolates, platelet isolates, megakaryocyte isolates, endothelial cell isolates, and osteocyte isolates) preferably 50 or more samples, prior to the determination of the expression level for the sample in question. The mean expression level of each of the genes assayed in the larger number of samples is determined and this is used as a baseline expression level for the gene(s) in question. The expression level of the gene determined for the test sample (absolute level of expression) is then divided by the mean expression value obtained for that gene. This provides a relative expression level and aids in identifying extreme cases of diseases and disorders such as obesity, coronary disorders (*e.g.*, atherosclerosis), neuronal disorders, pulmonary disorders, renal disorders, and bleeding disorders.

Preferably, the samples used in the baseline determination will be from diseased or from non-diseased cells of the appropriate cell type or tissue. The choice of the cell source is dependent on the use of the relative expression level. Using expression found in normal tissues as a mean expression score aids in validating whether the TANGO 253, TANGO 257, INTERCEPT 258, or TANGO 281 gene assayed is specific (versus normal cells). Such a use is particularly important in identifying whether a TANGO 253, TANGO 257, INTERCEPT 258, or TANGO 281 gene can serve as a target gene. In addition, as more data is accumulated, the mean expression value can be revised, providing improved relative expression values based on accumulated data. Expression data from cells provides a means for grading the severity of the disease or disorder state.

Another aspect of the invention pertains to monitoring the influence of agents (*e.g.*, drugs, compounds) on the expression or activity of TANGO 253, TANGO 257, INTERCEPT 258, or TANGO 281 in clinical trials. These and other agents are described in further detail in the following sections.

1. Diagnostic Assays

An exemplary method for detecting the presence or absence of a polypeptide or nucleic acid of the invention in a biological sample involves obtaining a biological sample

from a test subject and contacting the biological sample with a compound or an agent capable of detecting a polypeptide or nucleic acid (*e.g.*, mRNA, genomic DNA) of the invention such that the presence of a polypeptide or nucleic acid of the invention is detected in the biological sample. A preferred agent for detecting mRNA or genomic DNA encoding a polypeptide of the invention is a labeled nucleic acid probe capable of hybridizing to mRNA or genomic DNA encoding a polypeptide of the invention. The nucleic acid probe can be, for example, a full-length cDNA, such as the nucleic acid of SEQ ID NO:1, 2, 8, 9, 15, 16, 21, 22, 26, 27, 37, 38, 46, 47, 56 or 57, or a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to a mRNA or genomic DNA encoding a polypeptide of the invention. Other suitable probes for use in the diagnostic assays of the invention are described herein.

A preferred agent for detecting a polypeptide of the invention is an antibody capable of binding to a polypeptide of the invention, preferably an antibody with a detectable label. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (*e.g.*, Fab or $F(ab')_2$) can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (*i.e.*, physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently labeled streptavidin. The term "biological sample" is intended to include tissues, cells and biological fluids isolated from a subject, as well as tissues, cells and fluids present within a subject. That is, the detection method of the invention can be used to detect mRNA, protein, or genomic DNA in a biological sample *in vitro* as well as *in vivo*. For example, *in vitro* techniques for detection of mRNA include Northern hybridizations and *in situ* hybridizations. *In vitro* techniques for detection of a polypeptide of the invention include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence. *In vitro* techniques for detection of genomic DNA include Southern hybridizations. Furthermore, *in vivo* techniques for detection of a polypeptide of the invention include introducing into a subject a labeled antibody directed against the polypeptide. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

In one embodiment, the biological sample contains protein molecules from the test subject. Alternatively, the biological sample can contain mRNA molecules from the test

subject or genomic DNA molecules from the test subject. A preferred biological sample is a peripheral blood leukocyte sample isolated by conventional means from a subject.

In another embodiment, the methods further involve obtaining a control biological sample from a control subject, contacting the control sample with a compound or agent capable of detecting a polypeptide of the invention or mRNA or genomic DNA encoding a polypeptide of the invention, such that the presence of the polypeptide or mRNA or genomic DNA encoding the polypeptide is detected in the biological sample, and comparing the presence of the polypeptide or mRNA or genomic DNA encoding the polypeptide in the control sample with the presence of the polypeptide or mRNA or genomic DNA encoding the polypeptide in the test sample.

The invention also encompasses kits for detecting the presence of a polypeptide or nucleic acid of the invention in a biological sample (a test sample). Such kits can be used to determine if a subject is suffering from or is at increased risk of developing a disorder associated with aberrant expression of a polypeptide of the invention, as discussed, for example, in sections above relating to uses of the sequences of the invention.

For example, kits can be used to determine if a subject is suffering from or is at increased risk of disorders such as coronary disorders (*e.g.*, heart diseases and disorders such as atherosclerosis., coronary artery disease and plaque formation), and adipocyte-related disorders (*e.g.*, obesity), which are associated with aberrant TANGO 253 expression. In another example, kits can be used to determine if a subject is suffering from or is at increased risk of disorders such as coronary disorders (*e.g.*, heart diseases and disorders such as atherosclerosis, coronary artery disease and plague formation), olfactory disorders, neurological disorders (*e.g.*, neurodegenerative disorders, neuromuscular disorders, cognitive disorders, personality disorders, and motor disorder) and pulmonary disorders, (*e.g.*, cystic fibrosis), which are associated with aberrant TANGO 257 expression. In another example, kits can be used to determine if a subject is suffering from or is at increased risk of disorders such as Type I immunologic disorders, (*e.g.*, anaphylaxis and rhinitis), which are associated with aberrant INTERCEPT 258 expression. In another example, kits can be used to determine if a subject is suffering from or is at increased risk of disorders such as immunological disorders, (*e.g.* thrombocytopenia and platelet disorders), developmental disorders, coronary disorders, *e.g.*, ischemic heart disease or atherosclerosis, neurological disorders, (*e.g.*, head trauma and brain cancer), pulmonary disorders, (*e.g.*, lung cancer, cystic fibrosis and rheumatoid lung disease), kidney disorders, (*e.g.*, glomerulonephritis and end stage renal disease), autoimmune disorders, (*e.g.*, Crohn's disease) and embryonic disorders, which are associated with aberrant TANGO 281 expression. The kit, for example, can comprise a labeled compound

or agent capable of detecting the polypeptide or mRNA encoding the polypeptide in a biological sample and means for determining the amount of the polypeptide or mRNA in the sample (*e.g.*, an antibody which binds the polypeptide or an oligonucleotide probe which binds to DNA or mRNA encoding the polypeptide). Kits can also include instructions for observing that the tested subject is suffering from or is at risk of developing a disorder associated with aberrant expression of the polypeptide if the amount of the polypeptide or mRNA encoding the polypeptide is above or below a normal level.

For antibody-based kits, the kit can comprise, for example: (1) a first antibody (*e.g.*, attached to a solid support) which binds to a polypeptide of the invention; and, optionally, (2) a second, different antibody which binds to either the polypeptide or the first antibody and is conjugated to a detectable agent.

For oligonucleotide-based kits, the kit can comprise, for example: (1) an oligonucleotide, *e.g.*, a detectably labeled oligonucleotide, which hybridizes to a nucleic acid sequence encoding a polypeptide of the invention or (2) a pair of primers useful for amplifying a nucleic acid molecule encoding a polypeptide of the invention. The kit can also comprise, *e.g.*, a buffering agent, a preservative, or a protein stabilizing agent. The kit can also comprise components necessary for detecting the detectable agent (*e.g.*, an enzyme or a substrate). The kit can also contain a control sample or a series of control samples which can be assayed and compared to the test sample contained. Each component of the kit is usually enclosed within an individual container and all of the various containers are within a single package along with instructions for observing whether the tested subject is suffering from or is at risk of developing a disorder associated with aberrant expression of the polypeptide.

2. Prognostic Assays

The methods described herein can furthermore be utilized as diagnostic or prognostic assays to identify subjects having or at risk of developing a disease or disorder associated with aberrant expression or activity of a polypeptide of the invention. For example, the assays described herein, such as the preceding diagnostic assays or the following assays, can be utilized to identify a subject having or at risk of developing a disorder associated with aberrant expression or activity of a polypeptide of the invention, *e.g.*, coronary disorders, pulmonary disorders, kidney disorders or embryonic disorders. Alternatively, the prognostic assays can be utilized to identify a subject having or at risk for developing such a disease or disorder. Thus, the present invention provides a method in which a test sample is obtained from a subject and a polypeptide or nucleic acid (*e.g.*,

mRNA, genomic DNA) of the invention is detected, wherein the presence of the polypeptide or nucleic acid is diagnostic for a subject having or at risk of developing a disease or disorder associated with aberrant expression or activity of the polypeptide. As used herein, a "test sample" refers to a biological sample obtained from a subject of interest. For example, a test sample can be a biological fluid (*e.g.*, serum), cell sample, or tissue.

The prognostic assays described herein, for example, can be used to identify a subject having or at risk of developing disorders such as disorders discussed, for example, in Sections above relating to uses of the sequences of the invention.

For example, such disorders can include coronary disorders (*e.g.*, heart diseases and disorders such as atherosclerosis, coronary artery disease and plague formation) and adipocyte disorders (*e.g.*, obesity), which are associated with aberrant TANGO 253 expression. In another example, prognostic assays described herein, can be used to identify a subject having or at risk of developing disorders such as coronary disorders (*e.g.*, heart diseases and disorders such as atherosclerosis, coronary artery disease and plague formation), olfactory disorders, neurological disorders (*e.g.*, neurodegenerate disorders, neuromuscular disorders, cognitive disorders, personality disorders, and motor disorders), and pulmonary disorders, (*e.g.*, cystic fibrosis), which are associated with aberrant TANGO 257 expression. In another example, prognostic assays described herein, can be used to identify a subject having or at risk of developing disorders such as Type I immunologic disorders, (*e.g.*, anaphylaxis and rhinitis), which are associated with aberrant INTERCEPT 258 expression. In another example, prognostic assays described herein, for example, can be used to identify a subject having or at risk of developing disorders such as immunological disorders, (*e.g.* thrombocytopenia and platelet disorders), developmental disorders, coronary disorders, (*e.g.*, ischemic heart disease and atherosclerosis), neurological disorders, (*e.g.*, head trauma and brain cancer), pulmonary disorders, (*e.g.*, lung cancer, cystic fibrosis and rheumatoid lung disease), kidney disorders, (*e.g.*, glomerulonephritis and end stage renal disease), autoimmune disorders, (*e.g.*, Crohn's disease) and embryonic disorders, which are associated with aberrant TANGO 281 expression.

Furthermore, the prognostic assays described herein can be used to determine whether a subject can be administered an agent (*e.g.*, an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate) to treat a disease or disorder associated with aberrant expression or activity of a polypeptide of the invention. For example, such methods can be used to determine whether a subject can be effectively treated with a specific agent or class of agents (*e.g.*, agents of a type

which decrease activity of the polypeptide). Thus, the present invention provides methods for determining whether a subject can be effectively treated with an agent for a disorder associated with aberrant expression or activity of a polypeptide of the invention in which a test sample is obtained and the polypeptide or nucleic acid encoding the polypeptide is detected (*e.g.*, wherein the presence of the polypeptide or nucleic acid is diagnostic for a subject that can be administered the agent to treat a disorder associated with aberrant expression or activity of the polypeptide).

The methods of the invention can also be used to detect genetic lesions or mutations in a gene of the invention, thereby determining if a subject with the lesioned gene is at risk for a disorder characterized aberrant expression or activity of a polypeptide of the invention. In preferred embodiments, the methods include detecting, in a sample of cells from the subject, the presence or absence of a genetic lesion or mutation characterized by at least one of an alteration affecting the integrity of a gene encoding the polypeptide of the invention, or the mis-expression of the gene encoding the polypeptide of the invention. For example, such genetic lesions or mutations can be detected by ascertaining the existence of at least one of: 1) a deletion of one or more nucleotides from the gene; 2) an addition of one or more nucleotides to the gene; 3) a substitution of one or more nucleotides of the gene; 4) a chromosomal rearrangement of the gene; 5) an alteration in the level of a messenger RNA transcript of the gene; 6) an aberrant modification of the gene, such as of the methylation pattern of the genomic DNA; 7) the presence of a non-wild type splicing pattern of a messenger RNA transcript of the gene; 8) a non-wild type level of a the protein encoded by the gene; 9) an allelic loss of the gene; and 10) an inappropriate post-translational modification of the protein encoded by the gene. As described herein, there are a large number of assay techniques known in the art which can be used for detecting lesions in a gene.

In certain embodiments, detection of the lesion involves the use of a probe/primer in a polymerase chain reaction (PCR) (*see, e.g.*, U.S. Patent Nos. 4,683,195 and 4,683,202), such as anchor PCR or RACE PCR, or, alternatively, in a ligation chain reaction (LCR) (*see, e.g.*, Landegran et al. (1988) *Science* 241:1077-1080; and Nakazawa et al. (1994) *Proc. Natl. Acad. Sci. USA* 91:360-364), the latter of which can be particularly useful for detecting point mutations in a gene (*see, e.g.*, Abravaya et al. (1995) *Nucleic Acids Res.* 23:675-682). This method can include the steps of collecting a sample of cells from a patient, isolating nucleic acid (*e.g.*, genomic, mRNA or both) from the cells of the sample, contacting the nucleic acid sample with one or more primers which specifically hybridize to the selected gene under conditions such that hybridization and amplification of the gene (if present) occurs, and detecting the presence or absence of an

amplification product, or detecting the size of the amplification product and comparing the length to a control sample. It is anticipated that PCR and/or LCR may be desirable to use as a preliminary amplification step in conjunction with any of the techniques used for detecting mutations described herein.

Alternative amplification methods include: self sustained sequence replication (Guatelli et al. (1990) *Proc. Natl. Acad. Sci. USA* 87:1874-1878), transcriptional amplification system (Kwoh, et al. (1989) *Proc. Natl. Acad. Sci. USA* 86:1173-1177), Q-Beta Replicase (Lizardi et al. (1988) *Bio/Technology* 6:1197), or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers.

In an alternative embodiment, mutations in a selected gene from a sample cell can be identified by alterations in restriction enzyme cleavage patterns. For example, sample and control DNA is isolated, amplified (optionally), digested with one or more restriction endonucleases, and fragment length sizes are determined by gel electrophoresis and compared. Differences in fragment length sizes between sample and control DNA indicates mutations in the sample DNA. Moreover, the use of sequence specific ribozymes (*see*, *e.g.*, U.S. Patent No. 5,498,531) can be used to score for the presence of specific mutations by development or loss of a ribozyme cleavage site.

In other embodiments, genetic mutations can be identified by hybridizing a sample and control nucleic acids, *e.g.*, DNA or RNA, to high density arrays containing hundreds or thousands of oligonucleotides probes (Cronin et al. (1996) *Human Mutation* 7:244-255; Kozal et al. (1996) *Nature Medicine* 2:753-759). For example, genetic mutations can be identified in two-dimensional arrays containing light-generated DNA probes as described in Cronin et al., *supra*. Briefly, a first hybridization array of probes can be used to scan through long stretches of DNA in a sample and control to identify base changes between the sequences by making linear arrays of sequential overlapping probes. This step allows the identification of point mutations. This step is followed by a second hybridization array that allows the characterization of specific mutations by using smaller, specialized probe arrays complementary to all variants or mutations detected. Each mutation array is composed of parallel probe sets, one complementary to the wild-type gene and the other complementary to the mutant gene.

In yet another embodiment, any of a variety of sequencing reactions known in the art can be used to directly sequence the selected gene and detect mutations by comparing

the sequence of the sample nucleic acids with the corresponding wild-type (control) sequence. Examples of sequencing reactions include those based on techniques developed by Maxim and Gilbert ((1977) *Proc. Natl. Acad. Sci. USA* 74:560) or Sanger ((1977) *Proc. Natl. Acad. Sci. USA* 74:5463). It is also contemplated that any of a variety of automated sequencing procedures can be utilized when performing the diagnostic assays ((1995) *Bio/Techniques* 19:448), including sequencing by mass spectrometry (*see, e.g.*, PCT Publication No. WO 94/16101; Cohen et al. (1996) *Adv. Chromatogr.* 36:127-162; and Griffin et al. (1993) *Appl. Biochem. Biotechnol.* 38:147-159).

Other methods for detecting mutations in a selected gene include methods in which protection from cleavage agents is used to detect mismatched bases in RNA/RNA or RNA/DNA heteroduplexes (Myers et al. (1985) *Science* 230:1242). In general, the technique of mismatch cleavage entails providing heteroduplexes formed by hybridizing (labeled) RNA or DNA containing the wild-type sequence with potentially mutant RNA or DNA obtained from a tissue sample. The double-stranded duplexes are treated with an agent which cleaves single-stranded regions of the duplex such as which will exist due to basepair mismatches between the control and sample strands. RNA/DNA duplexes can be treated with RNase to digest mismatched regions, and DNA/DNA hybrids can be treated with S1 nuclease to digest mismatched regions.

In other embodiments, either DNA/DNA or RNA/DNA duplexes can be treated with hydroxylamine or osmium tetroxide and with piperidine in order to digest mismatched regions. After digestion of the mismatched regions, the resulting material is then separated by size on denaturing polyacrylamide gels to determine the site of mutation. *See, e.g.*, Cotton et al. (1988) *Proc. Natl. Acad. Sci. USA* 85:4397; Saleeba et al. (1992) *Methods Enzymol.* 217:286-295. In a preferred embodiment, the control DNA or RNA can be labeled for detection.

In still another embodiment, the mismatch cleavage reaction employs one or more proteins that recognize mismatched base pairs in double-stranded DNA (so called "DNA mismatch repair" enzymes) in defined systems for detecting and mapping point mutations in cDNAs obtained from samples of cells. For example, the mutY enzyme of E. coli cleaves A at G/A mismatches and the thymidine DNA glycosylase from HeLa cells cleaves T at G/T mismatches (Hsu et al. (1994) *Carcinogenesis* 15:1657-1662). According to an exemplary embodiment, a probe based on a selected sequence, *e.g.*, a wild-type sequence, is hybridized to a cDNA or other DNA product from a test cell(s). The duplex is treated with a DNA mismatch repair enzyme, and the cleavage products, if any, can be detected from electrophoresis protocols or the like. *See, e.g.*, U.S. Patent No. 5,459,039.

In other embodiments, alterations in electrophoretic mobility will be used to identify mutations in genes. For example, single strand conformation polymorphism (SSCP) may be used to detect differences in electrophoretic mobility between mutant and wild type nucleic acids (Orita et al. (1989) *Proc. Natl. Acad. Sci. USA* 86:2766; *see also* Cotton (1993) *Mutat. Res.* 285:125-144; Hayashi (1992) *Genet. Anal. Tech. Appl.* 9:73-79). Single-stranded DNA fragments of sample and control nucleic acids will be denatured and allowed to renature. The secondary structure of single-stranded nucleic acids varies according to sequence, and the resulting alteration in electrophoretic mobility enables the detection of even a single base change. The DNA fragments may be labeled or detected with labeled probes. The sensitivity of the assay may be enhanced by using RNA (rather than DNA), in which the secondary structure is more sensitive to a change in sequence. In a preferred embodiment, the subject method utilizes heteroduplex analysis to separate double stranded heteroduplex molecules on the basis of changes in electrophoretic mobility (Keen et al. (1991) *Trends Genet.* 7:5).

In yet another embodiment, the movement of mutant or wild-type fragments in polyacrylamide gels containing a gradient of denaturant is assayed using denaturing gradient gel electrophoresis (DGGE) (Myers et al. (1985) *Nature* 313:495). When DGGE is used as the method of analysis, DNA will be modified to insure that it does not completely denature, for example by adding a 'GC clamp of approximately 40 bp of high-melting GC-rich DNA by PCR. In a further embodiment, a temperature gradient is used in place of a denaturing gradient to identify differences in the mobility of control and sample DNA (Rosenbaum and Reissner (1987) *Biophys. Chem.* 265:12753).

Examples of other techniques for detecting point mutations include, but are not limited to, selective oligonucleotide hybridization, selective amplification, or selective primer extension. For example, oligonucleotide primers may be prepared in which the known mutation is placed centrally and then hybridized to target DNA under conditions which permit hybridization only if a perfect match is found (Saiki et al. (1986) *Nature* 324:163); Saiki et al. (1989) *Proc. Natl. Acad. Sci. USA* 86:6230). Such allele specific oligonucleotides are hybridized to PCR amplified target DNA or a number of different mutations when the oligonucleotides are attached to the hybridizing membrane and hybridized with labeled target DNA.

Alternatively, allele specific amplification technology which depends on selective PCR amplification may be used in conjunction with the instant invention. Oligonucleotides used as primers for specific amplification may carry the mutation of interest in the center of the molecule (so that amplification depends on differential hybridization) (Gibbs et al. (1989) *Nucleic Acids Res.* 17:2437-2448) or at the extreme 3'

end of one primer where, under appropriate conditions, mismatch can prevent or reduce polymerase extension (Prossner (1993) *Tibtech* 11:238). In addition, it may be desirable to introduce a novel restriction site in the region of the mutation to create cleavage-based detection (Gasparini et al. (1992) *Mol. Cell Probes* 6:1). It is anticipated that in certain embodiments amplification may also be performed using Taq ligase for amplification (Barany (1991) *Proc. Natl. Acad. Sci. USA* 88:189). In such cases, ligation will occur only if there is a perfect match at the 3' end of the 5' sequence making it possible to detect the presence of a known mutation at a specific site by looking for the presence or absence of amplification.

The methods described herein may be performed, for example, by utilizing pre-packaged diagnostic kits comprising at least one probe nucleic acid or antibody reagent described herein, which may be conveniently used, *e.g.*, in clinical settings to diagnose patients exhibiting symptoms or family history of a disease or illness involving a gene encoding a polypeptide of the invention. Furthermore, any cell type or tissue, *e.g.*, chondrocytes, in which the polypeptide of the invention is expressed may be utilized in the prognostic assays described herein.

3. Pharmacogenomics

Agents, or modulators which have a stimulatory or inhibitory effect on activity or expression of a polypeptide of the invention as identified by a screening assay described herein can be administered to individuals to treat (prophylactically or therapeutically) disorders associated with aberrant activity of the polypeptide. In conjunction with such treatment, the pharmacogenomics (i.e., the study of the relationship between an individual's genotype and that individual's response to a foreign compound or drug) of the individual may be considered. Differences in metabolism of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, the pharmacogenomics of the individual permits the selection of effective agents (*e.g.*, drugs) for prophylactic or therapeutic treatments based on a consideration of the individual's genotype. Such pharmacogenomics can further be used to determine appropriate dosages and therapeutic regimens. Accordingly, the activity of a polypeptide of the invention, expression of a nucleic acid of the invention, or mutation content of a gene of the invention in an individual can be determined to thereby select appropriate agent(s) for therapeutic or prophylactic treatment of the individual.

Pharmacogenomics deals with clinically significant hereditary variations in the response to drugs due to altered drug disposition and abnormal action in affected persons. *See, e.g.*, Linder (1997) *Clin. Chem.* 43(2):254-266. In general, two types of pharmacogenetic conditions can be differentiated. Genetic conditions transmitted as a single factor altering the way drugs act on the body are referred to as "altered drug action." Genetic conditions transmitted as single factors altering the way the body acts on drugs are referred to as "altered drug metabolism". These pharmacogenetic conditions can occur either as rare defects or as polymorphisms. For example, glucose-6-phosphate dehydrogenase deficiency (G6PD) is a common inherited enzymopathy in which the main clinical complication is haemolysis after ingestion of oxidant drugs (anti-malarials, sulfonamides, analgesics, nitrofurans) and consumption of fava beans.

As an illustrative embodiment, the activity of drug metabolizing enzymes is a major determinant of both the intensity and duration of drug action. The discovery of genetic polymorphisms of drug metabolizing enzymes (*e.g.*, N-acetyltransferase 2 (NAT 2) and cytochrome P450 enzymes CYP2D6 and CYP2C19) has provided an explanation as to why some patients do not obtain the expected drug effects or show exaggerated drug response and serious toxicity after taking the standard and safe dose of a drug. These polymorphisms are expressed in two phenotypes in the population, the extensive metabolizer (EM) and poor metabolizer (PM). The prevalence of PM is different among different populations. For example, the gene coding for CYP2D6 is highly polymorphic and several mutations have been identified in PM, which all lead to the absence of functional CYP2D6. Poor metabolizers of CYP2D6 and CYP2C19 quite frequently experience exaggerated drug response and side effects when they receive standard doses. If a metabolite is the active therapeutic moiety, a PM will show no therapeutic response, as demonstrated for the analgesic effect of codeine mediated by its CYP2D6-formed metabolite morphine. The other extreme are the so called ultra-rapid metabolizers who do not respond to standard doses. Recently, the molecular basis of ultra-rapid metabolism has been identified to be due to CYP2D6 gene amplification.

Thus, the activity of a polypeptide of the invention, expression of a nucleic acid encoding the polypeptide, or mutation content of a gene encoding the polypeptide in an individual can be determined to thereby select appropriate agent(s) for therapeutic or prophylactic treatment of the individual. In addition, pharmacogenetic studies can be used to apply genotyping of polymorphic alleles encoding drug-metabolizing enzymes to the identification of an individual's drug responsiveness phenotype. This knowledge, when applied to dosing or drug selection, can avoid adverse reactions or therapeutic failure and thus enhance therapeutic or prophylactic efficiency when treating a subject with a

modulator of activity or expression of the polypeptide, such as a modulator identified by one of the exemplary screening assays described herein.

4. Monitoring of Effects During Clinical Trials

Monitoring the influence of agents (*e.g.*, drugs, compounds) on the expression or activity of a polypeptide of the invention (*e.g.*, the ability to modulate aberrant cell proliferation chemotaxis, and/or differentiation) can be applied not only in basic drug screening, but also in clinical trials. For example, the effectiveness of an agent, as determined by a screening assay as described herein, to increase gene expression, protein levels or protein activity, can be monitored in clinical trials of subjects exhibiting decreased gene expression, protein levels, or protein activity. Alternatively, the effectiveness of an agent, as determined by a screening assay, to decrease gene expression, protein levels or protein activity, can be monitored in clinical trials of subjects exhibiting increased gene expression, protein levels, or protein activity. In such clinical trials, expression or activity of a polypeptide of the invention and preferably, that of other polypeptide that have been implicated in for example, a cellular proliferation disorder, can be used as a marker of the immune responsiveness of a particular cell.

For example, and not by way of limitation, genes, including those of the invention, that are modulated in cells by treatment with an agent (*e.g.*, compound, drug or small molecule) which modulates activity or expression of a polypeptide of the invention (*e.g.*, as identified in a screening assay described herein) can be identified. Thus, to study the effect of agents on cellular proliferation disorders, for example, in a clinical trial, cells can be isolated and RNA prepared and analyzed for the levels of expression of a gene of the invention and other genes implicated in the disorder. The levels of gene expression (i.e., a gene expression pattern) can be quantified by Northern blot analysis or RT-PCR, as described herein, or alternatively by measuring the amount of protein produced, by one of the methods as described herein, or by measuring the levels of activity of a gene of the invention or other genes. In this way, the gene expression pattern can serve as a marker, indicative of the physiological response of the cells to the agent. Accordingly, this response state may be determined before, and at various points during, treatment of the individual with the agent.

In a preferred embodiment, the present invention provides a method for monitoring the effectiveness of treatment of a subject with an agent (*e.g.*, an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate identified by the screening assays described herein) comprising the steps of (i) obtaining a

pre-administration sample from a subject prior to administration of the agent; (ii) detecting the level of the polypeptide or nucleic acid of the invention in the preadministration sample; (iii) obtaining one or more post-administration samples from the subject; (iv) detecting the level the of the polypeptide or nucleic acid of the invention in the post-administration samples; (v) comparing the level of the polypeptide or nucleic acid of the invention in the pre-administration sample with the level of the polypeptide or nucleic acid of the invention in the post-administration sample or samples; and (vi) altering the administration of the agent to the subject accordingly. For example, increased administration of the agent may be desirable to increase the expression or activity of the polypeptide to higher levels than detected, i.e., to increase the effectiveness of the agent. Alternatively, decreased administration of the agent may be desirable to decrease expression or activity of the polypeptide to lower levels than detected, i.e., to decrease the effectiveness of the agent.

C. Methods of Treatment

The present invention provides for both prophylactic and therapeutic methods of treating a subject at risk of (or susceptible to) a disorder or having a disorder associated with aberrant expression or activity of a polypeptide of the invention, as discussed, for example, in sections above relating to uses of the sequences of the invention.

For example, disorders characterized by aberrant expression or activity of the polypeptides of the invention include immunologic disorders, coronary disorders, pulmonary disorders, neurological disorders, kidney disorders, and autoimmune disorders. The nucleic acids, polypeptides, and modulators thereof of the invention can be used to treat immunologic diseases and disorders, including but not limited to, allergic disorders (*e.g.*, anaphylaxis and allergic asthma) autoimmune and inflammatory disorders (*e.g.*, atopic dermatitis). Polypeptides of the invention can be used to treat diseases associated with bacterial infection (*e.g.*, tuberculosis, *e.g.*, pulmonary tuberculosis), inflammatory arthropathy, and bone and cartilage degenerative diseases and disorders (*e.g.*, arthritis, *e.g.*, rheumatoid arthritis). Polypeptides of the invention can be used to treat pulmonary disorders such as lung cancer, cystic fibrosis and rheumatoid lung diseases. Polypeptides of the invention can be used to treat coronary disorders, such as ischemic heart disease, atherosclerosis and plague formation. Polypeptides of the invention can also be used to treat neurological disorders such as neurodegenerate disorders, neuromuscular disorders and cognitive disorders. Polypeptides of the invention can also be used to treat kidney disorders such as glomerulonephritis and end stage renal disease. Further, polypeptides of

the invention can be used to treat autoimmune disorders such as Crohns disease, and other disorders described herein.

1. Prophylactic Methods

In one aspect, the invention provides a method for preventing in a subject, a disease or condition associated with an aberrant expression or activity of a polypeptide of the invention, by administering to the subject an agent which modulates expression or at least one activity of the polypeptide. Subjects at risk for a disease which is caused or contributed to by aberrant expression or activity of a polypeptide of the invention can be identified by, for example, any or a combination of diagnostic or prognostic assays as described herein. Administration of a prophylactic agent can occur prior to the manifestation of symptoms characteristic of the aberrancy, such that a disease or disorder is prevented or, alternatively, delayed in its progression. Depending on the type of aberrancy, for example, an agonist or antagonist agent can be used for treating the subject. For example, an antagonist of a TANGO 253, TANGO 257, INTERCEPT 258 or TANGO 281 proteins may be used to treat an immunologic disorder, *e.g.*, rheumatoid arthritis. The appropriate agent can be determined based on screening assays described herein.

2. Therapeutic Methods

Another aspect of the invention pertains to methods of modulating expression or activity of a polypeptide of the invention for therapeutic purposes. The modulatory method of the invention involves contacting a cell with an agent that modulates one or more of the activities of the polypeptide. An agent that modulates activity can be an agent as described herein, such as a nucleic acid or a protein, a naturally-occurring cognate ligand of the polypeptide, a peptide, a peptidomimetic, or other small molecule. In one embodiment, the agent stimulates one or more of the biological activities of the polypeptide. Examples of such stimulatory agents include the active polypeptide of the invention and a nucleic acid molecule encoding the polypeptide of the invention that has been introduced into the cell. In another embodiment, the agent inhibits one or more of the biological activities of the polypeptide of the invention. Examples of such inhibitory agents include antisense nucleic acid molecules and antibodies. These modulatory methods can be performed *in vitro* (*e.g.*, by culturing the cell with the agent) or, alternatively, *in vivo* (*e.g.*, by administering the agent to a subject). As such, the present invention provides methods of treating an individual afflicted with a disease or disorder characterized by aberrant expression or activity of a polypeptide of the invention. In one

embodiment, the method involves administering an agent (*e.g.*, an agent identified by a screening assay described herein), or combination of agents that modulates (*e.g.*, upregulates or downregulates) expression or activity. In another embodiment, the method involves administering a polypeptide of the invention or a nucleic acid molecule of the invention as therapy to compensate for reduced or aberrant expression or activity of the polypeptide.

Stimulation of activity is desirable in situations in which activity or expression is abnormally low or downregulated and/or in which increased activity is likely to have a beneficial effect. Conversely, inhibition of activity is desirable in situations in which activity or expression is abnormally high or upregulated and/or in which decreased activity is likely to have a beneficial effect.

This invention is further illustrated by the following examples which should not be construed as limiting. The contents of all references, patents and published patent applications cited throughout this application are hereby incorporated by reference.

<u>Deposit of Clones</u>

Clones containing cDNA molecules encoding human TANGO 253, (clone EpT253) human TANGO 257 (EpT257), human INTERCEPT 258 (clone EpT258) and human TANGO 281 (clone EpT 281) were deposited with the American Type Culture Collection, 10801 University Boulevard, Manassas, VA, 20110-2209, on April 21, 1999 as Accession Number 207222, as part of a composite deposit representing a mixture of strains, each carrying one recombinant plasmid harboring a particular cDNA clone.

For this composite deposit, to distinguish the strains and isolate a strain harboring a particular cDNA clone, an aliquot of the mixture can be streaked out to single colonies on nutrient medium (*e.g.*, LB plates) supplemented with 100g/ml ampicillin, single colonies grown, and then plasmid DNA extracted using a standard minipreparation procedure. Next, a sample of the DNA minipreparation can be digested with a combination of the restriction enzymes *Sal*I, *Not*I, *Xba*I and *Ecor*V and the resultant products resolved on a 0.8% agarose gel using standard DNA electrophoresis conditions. The digest liberates fragments as follows:

Human TANGO 253 (clone EpT253): 1.3 kb

Human TANGO 257 (clone EpT257): 1.8 kb

Human INTERCEPT 258 (clone EpT258): 1.0 kb and 0.85 kb (human INTERCEPT 258 has a *Ecor*V cut site at about bp 1004).

Human TANGO 281 (clone EpT281): 0.9 kb and 0.9kb (human TANGO 281 Has an *Xba*I cut site at about bp 900).

The identity of the strains can be inferred from the fragments liberated.

Clones containing cDNA molecules encoding mouse INTERCEPT 258 were deposited with the American Type Culture Collection (Manassas, VA) on April 21, 1999 as Accession Number 207221, as part of a composite deposit representing a mixture of five strains, each carrying one recombinant plasmid harboring a particular cDNA clone.

To distinguish the strains and isolate a strain harboring a particular cDNA clone, an aliquot of the mixture can be streaked out to single colonies on nutrient medium (e.g., LB plates) supplemented with 100μg/ml ampicillin, single colonies grown, and then plasmid DNA extracted using a standard minipreparation procedure. Next, a sample of the DNA minipreparation can be digested with a combination of the restriction enzymes *Sal*I, and *Not*I, and the resultant products resolved on a 0.8% agarose gel using standard DNA electrophoresis conditions. The digest liberates fragments as follows:

Mouse INTERCEPT 258 (clone EpT258): 1.8 kb

The identity of the strains can be inferred from the fragments liberated.

A clone containing a cDNA molecule encoding mouse TANGO 253 (Clone EpTm 253) was deposited with American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209, on April 21, 1999 as Accession Number 207215.

A clone containing a cDNA molecule encoding mouse TANGO 257 (Clone EpTm 257) was deposited with American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209, on April 21, 1999 as Accession Number 207217.

A clone containing a cDNA molecule encoding mouse TANGO 281 (Clone EpTm 281) was deposited with American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209, on June 15, 1999 as patent deposit Number PTA-224.

All publications, patents and patent applications mentioned in this specification are herein incorporated by reference into the specification to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference.

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

MICROORGANISMS

Optional Sheet in connection with the microorganism referred to on pages ___, lines _____ of the description '

A. IDENTIFICATION OF DEPOSIT '

Further deposits are identified on an additional sheet '

Name of depositary institution '

American Type Culture Collection

Address of depositary institution (including postal code and country) '

10801 University Blvd.
Manassas, VA 20110-2209
US

Date of deposit ' April 21, 1999 Accession Number ' 207215

B. ADDITIONAL INDICATIONS ' (leave blank if not applicable). This information is continued on a separate attached sheet

C. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE ' (if the indications are not all designated States)

D. SEPARATE FURNISHING OF INDICATIONS ' (leave blank if not applicable)

The indications listed below will be submitted to the International Bureau later ' (Specify the general nature of the indications e.g., "Accession Number of Deposit")

E. ☐ This sheet was received with the International application when filed (to be checked by the receiving Office)

(Authorized Officer)

☐ The date of receipt (from the applicant) by the International Bureau '

was

(Authorized Officer)

Form PCT/RO/134 (January 1981)

International Application No: PCT/

Form PCT/RO/134 (cont.)

American Type Culture Collection

10801 University Blvd.
Manassas, VA 20110-2209
US

Accession No.	Date of Deposit
207217	April 21, 1999
207221	April 21, 1999
207222	April 21, 1999
207222	April 21, 1999
207222	April 21, 1999
207222	April 21, 1999
PTA-224	June 15, 1999

What is claimed is:

1. An isolated nucleic acid molecule selected from the group consisting of:

a) a nucleic acid molecule comprising a nucleotide sequence which is at least 45% identical to the nucleotide sequence of SEQ ID NO:1, 2, 26, 27, 46, 47, the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207222, or a complement thereof;

b) a nucleic acid molecule comprising a fragment of at least 300 nucleotides of the nucleotide sequence of SEQ ID NO:1, 2, 15, 16, 26, 27, 46, 47, the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207222, or a complement thereof;

c) a nucleic acid molecule which encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:3, 17, 28, 48, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207222;

d) a nucleic acid molecule which encodes a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:3, 28, 48, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207222, wherein the fragment comprises at least 15 contiguous amino acids of SEQ ID NO:3, 28, 48, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207222;

e) a nucleic acid molecule which encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:3, 17, 28, 48, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207222, wherein the nucleic acid molecule hybridizes to a nucleic acid molecule comprising SEQ ID NO:2, 16, 27, 47, or a complement thereof under stringent conditions;

f) a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID NO:21, 22, the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207217, or a complement thereof;

g) a nucleic acid molecule comprising a fragment of at least 300 nucleotides of the nucleotide sequence of SEQ ID NO:21, 22, the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207217, or a complement thereof;

h) a nucleic acid molecule which encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:23, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207217;

i) a nucleic acid molecule which encodes a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:23, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207217, wherein the fragment comprises at least 360 contiguous amino acids of SEQ ID NO:23, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207217;

j) a nucleic acid molecule which encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:23, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207217, wherein the nucleic acid molecule hybridizes to a nucleic acid molecule comprising SEQ ID NO:22, or a complement thereof under stringent conditions;

k) a nucleic acid molecule comprising a nucleotide sequence which is at least 45% identical to the nucleotide sequence of SEQ ID NO:37, 38, the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207221, or a complement thereof;

l) a nucleic acid molecule comprising a fragment of at least 300 nucleotides of the nucleotide sequence of SEQ ID NO:37, 38, the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207221, or a complement thereof;

m) a nucleic acid molecule which encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:39, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207221;

n) a nucleic acid molecule which encodes a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:39, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207221, wherein the fragment comprises at least 160 contiguous amino acids of SEQ ID NO:39, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207221;

o) a nucleic acid molecule which encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:39, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC® as

Accession Number 207217, wherein the nucleic acid molecule hybridizes to a nucleic acid molecule comprising SEQ ID NO:38, or a complement thereof under stringent conditions;

p) a nucleic acid molecule comprising a nucleotide sequence which is at least 45% identical to the nucleotide sequence of SEQ ID NO:8, 9, the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207215, or a complement thereof;

q) a nucleic acid molecule comprising a fragment of at least 300 nucleotides of the nucleotide sequence of SEQ ID NO:8, 9, the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207215, or a complement thereof;

r) a nucleic acid molecule which encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:10, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207215;

s) a nucleic acid molecule which encodes a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:10, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207215, wherein the fragment comprises at least 15 contiguous amino acids of SEQ ID NO:10, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207215;

t) a nucleic acid molecule which encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:10, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207215, wherein the nucleic acid molecule hybridizes to a nucleic acid molecule comprising SEQ ID NO:9, or a complement thereof under stringent conditions;

u) a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID NO:15, 16, the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207222, or a complement thereof;

v) a nucleic acid molecule which encodes a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:17, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207222, wherein the fragment comprises at least 360 contiguous amino acids of SEQ ID NO:17, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207222.

w) a nucleic acid molecule comprising a nucleotide sequence which is at least 45% identical to the nucleotide sequence of SEQ ID NO:56, 57, the cDNA insert of the plasmid deposited with the ATCC® as patent deposit Number PTA-224, or a complement thereof;

x) a nucleic acid molecule comprising a fragment of at least 300 nucleotides of the nucleotide sequence of SEQ ID NO:56, 57, the cDNA insert of the plasmid deposited with the ATCC® as patent deposit Number PTA-224, or a complement thereof;

y) a nucleic acid molecule which encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:58, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC® as patent deposit Number PTA-224;

z) a nucleic acid molecule which encodes a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:58, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC® as patent deposit Number PTA-224, wherein the fragment comprises at least 15 contiguous amino acids of SEQ ID NO:58, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC® as patent deposit Number PTA-224;

aa) a nucleic acid molecule which encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:58, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC® as patent deposit Number PTA-224, wherein the nucleic acid molecule hybridizes to a nucleic acid molecule comprising SEQ ID NO:57, or a complement thereof under stringent conditions.

2. The isolated nucleic acid molecule of claim 1, which is selected from the group consisting of:

a) a nucleic acid comprising the nucleotide sequence of SEQ ID NO:1, 2, 15, 16, 26, 27, 46, 47, the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207222, or a complement thereof;

b) a nucleic acid molecule which encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:3, 17, 28, 48, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207222;

c) a nucleic acid comprising the nucleotide sequence of SEQ ID NO:21, 22, the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207217, or a complement thereof;

d) a nucleic acid molecule which encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:23, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207217;

e) a nucleic acid comprising the nucleotide sequence of SEQ ID NO:37, 38, the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207221, or a complement thereof;

f) a nucleic acid molecule which encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:39, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207221;

g) a nucleic acid comprising the nucleotide sequence of SEQ ID NO:8, 9, the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207215, or a complement thereof;

h) a nucleic acid molecule which encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:10, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207222.

i) a nucleic acid comprising the nucleotide sequence of SEQ ID NO:56, 57, the cDNA insert of the plasmid deposited with the ATCC® as patent deposit Number PTA-224, or a complement thereof;

j) a nucleic acid molecule which encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:58, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC® as patent deposit Number PTA-224.

3. The nucleic acid molecule of claim 1 further comprising vector nucleic acid sequences.

4. The nucleic acid molecule of claim 1 further comprising nucleic acid sequences encoding a heterologous polypeptide.

5. A host cell which contains the nucleic acid molecule of claim 1.

6. The host cell of claim 5 which is a mammalian host cell.

7. A non-human mammalian host cell containing the nucleic acid molecule of claim 1.

8. An isolated polypeptide selected from the group consisting of:

a) a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:3, 10, 17, 23, 28, 39, 48, 58, wherein the fragment comprises at least 15 contiguous amino acids of SEQ ID NO:3, 10, 17, 23, 28, 39, 48, 58;

b) a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:3, 10, 17, 23, 28, 39, 48, 58, or the amino acid sequence encoded by the cDNA insert of plasmids deposited with the ATCC® as Accession Number 207222, Accession Number 207215, Accession Number 207217, Accession Number 207221, patent deposit Number PTA-224 wherein the polypeptide is encoded by a nucleic acid molecule which hybridizes to a nucleic acid molecule comprising SEQ ID NO:2, 9, 16, 22, 27, 38, 47, 57, or a complement thereof under stringent conditions; and

c) a polypeptide which is encoded by a nucleic acid molecule comprising a nucleotide sequence which is at least 45% identical to a nucleic acid comprising the nucleotide sequence of SEQ ID NO:2, 9, 27, 38, 47, 57, or at least 98% to a nucleic acid comprising the nucleotide sequence of SEQ ID NO:2, 9, 27, 38, 47, 57, or a complement thereof.

9. The isolated polypeptide of claim 8 comprising the amino acid sequence of SEQ ID NO:3, 10, 17, 23, 28, 39, 48, 58.

10. The polypeptide of claim 8 further comprising heterologous amino acid sequences.

11. An antibody which selectively binds to a polypeptide of claim 8.

12. A method for producing a polypeptide selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence of SEQ ID NO:3, 10, 17, 23, 28, 39, 48, 58, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207222, Accession Number

207215, Accession Number 207217, Accession Number 207221, or patent deposit Number PTA-224;

b) a polypeptide comprising a fragment of the amino acid sequence of SEQ ID NO:3, 10, 17, 23, 28, 39, 48, 58, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207222, Accession Number 207215, Accession Number 207217, Accession Number 207221, or patent deposit Number PTA-224, wherein the fragment comprises at least 15 contiguous amino acids of SEQ ID NO:3, 10, 17, 23, 28, 39, 48, 58, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207222, Accession Number 207215, Accession Number 207217, Accession Number 207221 or patent deposit Number PTA-224; and

c) a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:3, 10, 17, 23, 28, 39, 48, 58, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC® as Accession Number 207222, Accession Number 207215, Accession Number 207217, Accession Number 207221, or patent deposit Number PTA-224, wherein the polypeptide is encoded by a nucleic acid molecule which hybridizes to a nucleic acid molecule comprising SEQ ID NO:1, 8, 15, 21, 26, 37, 46, 56, or a complement thereof under stringent conditions;

comprising culturing the host cell of claim 5 under conditions in which the nucleic acid molecule is expressed.

13. A method for detecting the presence of a polypeptide of claim 8 in a sample, comprising:

a) contacting the sample with a compound which selectively binds to a polypeptide of claim 8; and

b) determining whether the compound binds to the polypeptide in the sample.

14. The method of claim 13, wherein the compound which binds to the polypeptide is an antibody.

15. A kit comprising a compound which selectively binds to a polypeptide of claim 8 and instructions for use.

16. A method for detecting the presence of a nucleic acid molecule of claim 1 in a sample, comprising the steps of:

a) contacting the sample with a nucleic acid probe or primer which selectively hybridizes to the nucleic acid molecule; and

b) determining whether the nucleic acid probe or primer binds to a nucleic acid molecule in the sample.

17. The method of claim 16, wherein the sample comprises mRNA molecules and is contacted with a nucleic acid probe.

18. A kit comprising a compound which selectively hybridizes to a nucleic acid molecule of claim 1 and instructions for use.

19. A method for identifying a compound which binds to a polypeptide of claim 8 comprising the steps of:

a) contacting a polypeptide, or a cell expressing a polypeptide of claim 8 with a test compound; and

b) determining whether the polypeptide binds to the test compound.

20. The method of claim 19, wherein the binding of the test compound to the polypeptide is detected by a method selected from the group consisting of:

a) detection of binding by direct detecting of test compound/polypeptide binding;

b) detection of binding using a competition binding assay;

c) detection of binding using an assay for TANGO 253, TANGO 257, INTERCEPT 258, TANGO 281-mediated signal transduction.

21. A method for modulating the activity of a polypeptide of claim 8 comprising contacting a polypeptide or a cell expressing a polypeptide of claim 8 with a compound which binds to the polypeptide in a sufficient concentration to modulate the activity of the polypeptide.

22. A method for identifying a compound which modulates the activity of a polypeptide of claim 8, comprising:

a) contacting a polypeptide of claim 8 with a test compound; and

b) determining the effect of the test compound on the activity of the polypeptide to thereby identify a compound which modulates the activity of the polypeptide.

GTCGACCCACGCGTCCGGGACTGGGGTGACGGCAGGGCAGGGGGCGCCTGGCCGGGGAGAAGCGCGGGGGCTGGAGCAC 79

CACCAACTGGAGGGTCCGGAGTAGCGAGCGCCCCGAAGGAGGCCATCGGGGAGCCGGGAGGGGGGACTGCGAGAGGACC 158

M R P L L V L L L L G L 12
CCGGCGTCCGGGCTCCCGGTGCCAGCGCT ATG AGG CCA CTC CTC GTC CTG CTG CTC CTG GGC CTG 223

A A G S P P L D D N K I P S L C P G H P 32
GCG GCC GGC TCG CCC CCA CTG GAC GAC AAC AAG ATC CCC AGC CTC TGC CCG GGG CAC CCC 283

G L P G T P G H H G S Q G L P G R D G R 52
GGC CTT CCA GGC ACG CCG GGC CAC CAT GGC AGC CAG GGC TTG CCG GGC CGC GAT GGC CGC 343

D G R D G A P G A P G E K G E G G R P G 72
GAC GGC CGC GAC GGC GCG CCC GGG GCT CCG GGA GAG AAA GGC GAG GGC GGG AGG CG GGA 403

L P G P R G D P G P R G E A G P A G P T 92
CTG CCG GGA CCT CGA GGG GAC CCC GGG CCG CGA GGA GAG GCG GGA CCC GCG GGG CCC ACC 463

G P A G E C S V P P R S A F S A K R S E 112
GGG CCT GCC GGG GAG TGC TCG GTG CCT CCG CGA TCC GCC TTC AGC GCC AAG CGC TCC GAG 523

S R V P P P S D A P L P F D R V L V N E 132
AGC CGG GTG CCT CCG CCG TCT GAC GCA CCC TTG CCC TTC GAC CGC GTG CTG GTG AAC GAG 583

Q G H Y D A V T G K F T C Q V P G V Y Y 152
CAG GGA CAT TAC GAC GCC GTC ACC GGC AAG TTC ACC TGC CAG GTG CCT GGG GTC TAC TAC 643

F A V H A T V Y R A S L Q F D L V K N G 172
TTC GCC GTC CAT GCC ACC GTC TAC CGG GCC AGC CTG CAG TTT GAT CTG GTG AAG AAT GGC 703

E S I A S F F Q F F G G W P K P A S L S 192
GAA TCC ATT GCC TCT TTC TTC CAG TTT TTC GGG GGG TGG CCC AAG CCA GCC TCG CTC TCG 763

G G A M V R L E P E D Q V W V Q V G V G 212
GGG GGG GCC ATG GTG AGG CTG GAG CCT GAG GAC CAA GTG TGG GTG CAG GTG GGT GTG GGT 823

D Y I G I Y A S I K T D S T F S G F L V 232
GAC TAC ATT GGC ATC TAT GCC AGC ATC AAG ACA GAC AGC ACC TTC TCC GGA TTT CTG GTG 883

Y S D W H S S P V F A * 244
TAC TCC GAC TGG CAC AGC TCC CCA GTC TTT GCT TAG 919

TGCCCACTGCAAAGTGAGCTCATGCTCTCACTCCTAGAAGGAGGGTGTGAGGCTGACAACCTGGTCATCCAGGAGGGCT 998

GGCCCCCCTGGAATATTGTGAATGACTAGGGAGGTGGGGTAGAGCACTCTCCGTCCTGCTGCTGGCAAGGAATGGGAAC 1077

FIG. 1A

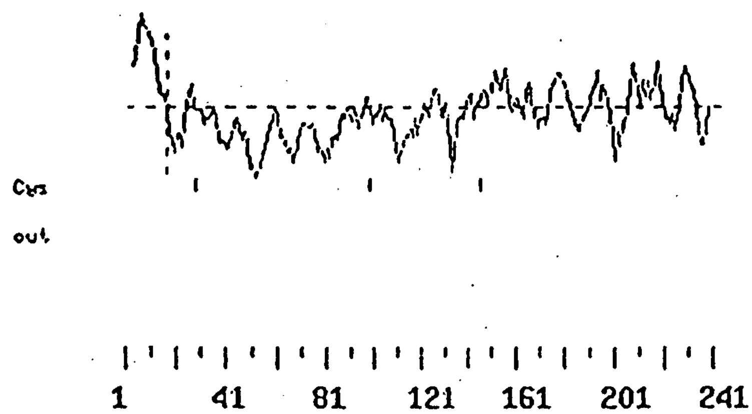
AGTGGCTGTCTGCGATCAGGTCTGGCAGCATGGGGCAGTGGCTGGATTTCTGCCCAAGACCAGAGGAGTGTGCTGTGCT 1156

GGCAAGTGTAAGTCCCCCAGTTGCTCTGGTCCAGGAGCCCACGGTGGGGTGCTCTCTTCCTGGTCCTCTGCTTCTCTGG 1235

ATCCTCCCCACCCCCTCCTGCTCCTGGGGCCGGCCCTTTTCTCAGAGATCACTCAATAAACCTAAGAACCCTCCAAAAA 1314

AAAAAAAAAAAAAAAGGGCGGCCGC 1339

FIG. 1B



MRPLLVLLLLGLAAGSPPLDDNKIPSLCPGHPGLPGTPGHHGSQGLPGRDGRDGRDGAPG
APGEKGEGGRPGLPGPRGDPGPRGEAGPAGPTGPAGECSVPPRSAFSAKRSESRVPPPSD
APLPFDRVLVNEQGHYDAVTGKFTCQVPGVYYFAVHATVYRASLQFDLVKNGESIASFFQ
FFGGWPKPASLSGGAMVRLEPEDQVWVQVGVGDYIGIYASIKTDSTFSGFLVYSDWHSSP
VFA

FIG. 2

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GTCGACCCACGCGTCCGCGCTGTGAAGCCAGCAAGGAGCAACCAGAAGCTAGGAGTCAGTCAGCAAGGACAGGGGCTGC  79

                                                      M   R   P   L   L   A      6
CTGCCTACAGACTACAAGAGAGGTTCCTGGAGTCTGAGCCTCCGGGGTCACCACC ATG AGG CCA CTT CTT GCC  152

 L   L   L   L   G   L   V   S   G   S   P   P   L   D   D   N   K   I   P   S    26
CTT CTG CTT CTG GGT CTG GTG TCA GGC TCT CCT CCT CTG GAC GAC AAC AAG ATC CCC AGC  212

 L   C   P   G   Q   P   G   L   P   G   T   P   G   H   H   G   S   Q   G   L    46
CTG TGT CCC GGG CAG CCC GGC CTT CCA GGC ACA CCA GGT CAC CAT GGC AGC CAA GGC CTG  272

 P   G   R   D   G   R   D   G   R   D   G   A   P   G   A   P   G   E   K   G    66
CCT GGC CGT GAC GGC CGT GAT GGC CGC GAC GGT GCA CCC GGA GCT CCG GGA GAG AAA GGC  332

 E   G   G   R   P   G   L   P   G   P   R   G   E   P   G   P   R   G   E   A    86
GAG GGC GGG AGA CCG GGA CTA CCT GGC CCA CGT GGG GAG CCC GGG CCG CGT GGA GAG GCA  392

 G   P   M   G   A   I   G   P   A   G   E   C   S   V   P   P   R   S   A   F   106
GGG CCC ATG GGG GCT ATC GGG CCT GCG GGG GAG TGC TCG GTA CCC CCA CGA TCA GCC TTC  452

 S   A   K   R   S   E   S   R   V   P   P   P   A   D   T   P   L   P   F   D   126
AGT GCC AAG CGA TCC GAG AGC CGG GTA CCT CCG CCA GCC GAC ACA CCC CTA CCT TTC GAC  512

 R   V   L   L   N   E   Q   G   H   Y   D   P   T   T   G   K   F   T   C   Q   146
CGT GTG CTG CTA AAT GAG CAG GGC CAT TAC GAC CCC ACT ACT GGC AAG TTC ACC TGC CAA  572

 V   P   G   V   Y   Y   F   A   V   H   A   T   V   Y   R   A   S   L   Q   F   166
GTG CCT GGC GTC TAC TAC TTT GCT GTG CAC GCC ACT GTC TAC CGG GCC AGC TTG CAG TTT  632

 D   L   V   K   N   G   Q   S   I   A   S   F   F   Q   Y   F   G   G   W   P   186
GAT CTT GTC AAA AAC GGG CAG TCC ATC GCC TCT TTC TTC CAG TAT TTT GGG GGG TGG CCC  692

 K   P   A   S   L   S   G   G   A   M   V   R   L   E   P   E   D   Q   V   W   206
AAG CCA GCC TCG CTC TCA GGG GGT GCG ATG GTA AGG CTA GAA CCT GAG GAC CAG GTG TGG  752

 V   Q   V   G   V   G   D   Y   I   G   I   Y   A   S   I   K   T   D   S   T   226
GTG CAG GTG GGC GTG GGT GAT TAC ATT GGC ATC TAT GCC AGC ATC AAG ACA GAC AGT ACC  812

 F   S   G   F   L   V   Y   S   D   W   H   S   S   P   V   F   A   *           244
TTC TCT GGA TTT CTC GTC TAT TCT GAC TGG CAC AGC TCC CCA GTC TTC GCT TAA          866

AACACAGTGAACCCGGAGCTGGCACTTGCTCCTCAGTGGAGGGTGTGACACTAACCCGCGCAGCGCATACCAGGAGGGC  945

TGGCCCCCTGGAATATTGTGAATGACTTAGGAAGAGAGGGAGCCACTTCCAGTCCCACTGCTGGCAATGAATGGAGACA  1024

GGCTGTCTGAGGTCAAGACAGCGTGGAGCAGTGGCTGGGTTTCTGCCCAGGACTTTAGAATGCAGTAGGCTGGCAGCTG  1103

TGGGTCCTGGCCCAGGACTCCAAGGTGGGATGCTCCATTCCTAGTCCTGTGTCCCCTCTAGGTCCCTGACTCCATCTCT  1182
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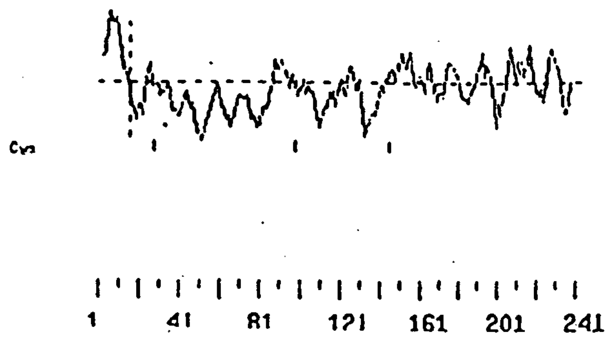
FIG. 3A

GCTGCTCCCAGGGCAGGCCTTTTTCTCAGAGGTCACTTAATAAACCTAAAATCCTCAAAAAAAAAAAAAAAGGGCGGCC 1261

GC 1263

FIG. 3B



>mT253
MRPLLALLLLGLVSGSPPLDDNKIPSLCPGQPGLPGTPGHHGSQGLPGRDGRDGRDGAPG
APGEKGEGGRPGLPGPRGEPGPRGEAGPMGAIGPAGECSVPPRSAFSAKRSESRVPPPAD
TPLPFDRVLLNEQGHYDPTTGKFTCQVPGVYYFAVHATVYRASLQFDLVKNGQSIASFFQ
YFGGWPKPASLSGGAMVRLEPEDQVWVQVGVGDYIGIYASIKTDSTFSGFLVYSDWHSSP
VFA

FIG. 4

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ALIGN calculates a global alignment of two sequences
 version 2.0uPlease cite: Myers and Miller, CABIOS (1989)
> hT253 a.a.                                      243 aa vs.
> mT253 a.a.                                      243 aa
scoring matrix: pam120.mat, gap penalties: -12/-4
93.8% identity;                Global alignment score: 1239

                10        20        30        40        50        60        70
inputs MRPLLVLLLLGLAAGSPPLDDNKIPSLCPGHPGLPGTPGHHGSQGLPGRDGRDGRDGAPGAPGEKGEGGR
       :::::.::::::..::::::::::::::::.:::::::::::::::::::::::::::::::::::::::
       MRPLLALLLLGLVSGSPPLDDNKIPSLCPGQPGLPGTPGHHGSQGLPGRDGRDGRDGAPGAPGEKGEGGR
                10        20        30        40        50        60        70

                80        90       100       110       120       130       140
inputs PGLPGPRGDPGPRGEAGPAGPTGPAGECSVPPRSAFSAKRSESRVPPPSDAPLPFDRVLVNEQGHYDAVT
       ::::::::.::::::::: :..::::::::::::::::::::::::::.:.::::::::.:::::::..:
       PGLPGPRGEPGPRGEAGPMGAIGPAGECSVPPRSAFSAKRSESRVPPPADTPLPFDRVLLNEQGHYDPTT
                80        90       100       110       120       130       140

               150       160       170       180       190       200       210
inputs GKFTCQVPGVYYFAVHATVYRASLQFDLVKNGESIASFFQFFGGWPKPASLSGGAMVRLEPEDQVWVQVG
       ::::::::::::::::::::::::::::::::.:::::::.:::::::::::::::::::::::::::::
       GKFTCQVPGVYYFAVHATVYRASLQFDLVKNGQSIASFFQYFGGWPKPASLSGGAMVRLEPEDQVWVQVG
               150       160       170       180       190       200       210

               220       230       240
inputs VGDYIGIYASIKTDSTFSGFLVYSDWHSSPVFA
       :::::::::::::::::::::::::::::::::
       VGDYIGIYASIKTDSTFSGFLVYSDWHSSPVFA
               220       230       240
```

FIG. 5

```
ALIGN calculates a global alignment of two sequences
 version 2.0uPlease cite: Myers and Miller, CABIOS (1989)
> hT253 a.a.                                            243 aa vs.
> SwissProt Q15848 - (untitled)                         244 aa
scoring matrix: pam120.mat, gap penalties: -12/-4
38.7% identity;           Global alignment score: 262

                 10        20        30        40        50        60
inputs MRPL-LVLLLLGLAA---GSPPLDDNKIPSL----CPG-HPGLPGTPGHHGSQGLPGRDGRDGRDGAPGA
       :  :  :::::.:..    .   . . . .:    : :  .:.:: :::.:..: :::: .  : :. :.
       MLLLGAVLLLLALPGHDQETTTQGPGVLLPLPKGACTGWMAGIPGHPGHNGAPGRDGRDGTPGEKGEKGD
               10        20        30        40        50        60        70

                70        80        90       100       110       120       130
inputs PGEKGEGGRPGLPGPRGDPGPRGEAGPAGPTGPAGECSVPPRSAFSAKRSESRVPPPSDAPLPFDRVLVN
       ::  :  :  :  :  :. :::: .:  :   : .:: .    :::::.   :. :   :  . :. : ... :
       PGLIGPKGDIGETGVPGAEGPRGFPGIQGRKGEPGEGAYVYRSAFSVGL-ETYVTIP-NMPIRFTKIFYN
                 80        90       100       110       120       130

              140       150       160       170       180       190       200
inputs EQGHYDAVTGKFTCQVPGVYYFAVHATVYRASLQFDLVKNGESIASFFQFFGGWPKPASLSGGAMVRLEP
       .:.:::. :::: :..::.:::: : :::    ... .: :.. ..     .. .       . .   ::.....::
       QQNHYDGSTGKFHCNIPGLYYFAYHITVYMKDVKVSLFKKDKAMLFTYDQYQE-NNVDQASGSVLLHLEV
      140       150       160       170       180       190       200

                210       220       230       240
inputs EDQVWVQV-GVGDYIGIYASIKTDSTFSGFLVYSDWHSSPVFA
        ::::.:: : :.  :.::.  .::::.:::.:     :..    .
       GDQVWLQVYGEGERNGLYADNDNDSTFTGFLLY---HDT---N
       210       220       230       240
```

FIG. 6A

```
ALIGN calculates a global alignment of two sequences
 version 2.0uPlease cite: Myers and Miller, CABIOS (1989)
> mT253 a.a.                                      243 aa vs.
> SwissProt Q15848 - (untitled)                   244 aa
scoring matrix: pam120.mat, gap penalties: -12/-4
38.3% identity;          Global alignment score: 264

               10        20                30         40        50        60
inputs MRPLLALLLLGLVSGSPPLDDNKIPSL--------CPG-QPGLPGTPGHHGSQGLPGRDGRDGRDGAPGA
       :  : :.:::  ..:  .   .. :..        : :  .:.:: :::.:..:  ::::  :  :. :.
       MLLLGAVLLLLALPGHDQETTTQGPGVLLPLPKGACTGWMAGIPGHPGHNGAPGRDGRDGTPGEKGEKGD
               10        20        30        40        50        60        70

               70        80        90       100       110       120       130
inputs PGEKGEGGRPGLPGPRGEPGPRGEAGPMGAIGPAGECSVPPRSAFSAKRSESRVPPPADTPLPFDRVLLN
       ::  :  :  :  :  :. :::: .:  :   : .:: .   :::::.   :. :  : . :. : ... :
       PGLIGPKGDIGETGVPGAEGPRGFPGIQGRKGEPGEGAYVYRSAFSVGL-ETYVTIP-NMPIRFTKIFYN
               80        90       100       110        120        130

              140       150       160       170       180       190       200
inputs EQGHYDPTTGKFTCQVPGVYYFAVHATVYRASLQFDLVKNGQSIASFFQYFGGWPKPASLSGGAMVRLEP
       .:.::: .:::: :..::.:::: : :::  ... .: :.....   ..  .    . .  ::.....::
       QQNHYDGSTGKFHCNIPGLYYFAYHITVYMKDVKVSLFKKDKAMLFTYDQYQE-NNVDQASGSVLLHLEV
      140       150       160       170       180       190        200

              210       220       230       240
inputs EDQVWVQV-GVGDYIGIYASIKTDSTFSGFLVYSDWHSSPVFA
        ::::.:: : :.  :.::.  .::::.:::.:   :..   .
       GDQVWLQVYGEGERNGLYADNDNDSTFTGFLLY---HDT---N
       210       220       230       240
```

FIG. 6B

```
ALIGN calculates a global alignment of two sequences
 version 2.0uPlease cite: Myers and Miller, CABIOS (1989)
> hT253 n.a.                                      1339 aa vs.
> adipocyte n.a. (AI417523)                        653 aa
scoring matrix: pam120.mat, gap penalties: -12/-4
29.1% identity;          Global alignment score: -1168

               10        20        30        40        50        60        70
inputs GTCGACCCACGCGTCCGGGACTGGGGTGACGGCAGGGCAGGGGGCGCCTGGCCGGGGAGAAGCGCGGGGG
        :  .      ::.:  : .:::    :.. :.   ::::     :. :..: :.  :..:   ::  ::.
       TTTTTT----GCAT--GTAACTTTTTATTGA---GGCA-----CAACAAGGCATTGTAACTTGCCTGGA
                  10          20          30              40        50

               80        90       100       110       120       130       140
inputs CTGGAGCACCACCAACTGGAGGGTCCGGAGTAGCGAGCGCCCCGAAGGAGGCCATCGGGGAGCCGGGAGG
       :: :::          .:.:        :.:. ::: .:::     :::            ::  .:  :.: ...
       CTTGAG--------GCAGT------CAGTTTAGTAAGCT----GAA---------CGTTAATACAGTTAA
         60                      70         80                       90

              150       160       170       180       190       200       210
inputs GGGGACTGCGAGAGGACCCCGGCGTCCGGGCTCCCGGTGCCAGCGCTATGAGGCCACTCCTCGTCCTGCT
       ::.  .  .:                            ::: :.:. :::.     :: ::          .:.
       GGATTAAG-----------------------------TGCAAACAATATA----CATTC--------ACA
     100                                     110        120

              220       230       240       250       260       270       280
inputs GCTCCTGGGCCTGGCGGCCGGCTCGCCCCCACTGGACGACAACAAGATCCCCAGCCTCTGCCCGGGGCAC
       :::  ::.  ::.:::.  ::::            ::..:: ::: .:      ::     :::: :.
       GCT--TGA--CTAGCGA--GGCT------------ACATCA-CAATTTATAAAG----TGCCAGA-----
      130          140                     150        160           170

              290       300       310       320       330       340       350
inputs CCCGGCCTTCCAGGCACGCCGGGCCACCATGGCAGCCAGGGCTTGCCGGGCCGCGATGGCCGCGACGGCC
              ::  ::     :: ..       .:: ::  ::  :::::            ..:    :.:
       -------TT--AGT---GCTAA------TTGTCATTCA--GCTTG---------ATTTTTCAC-------
                          180                190                 200

              360       370       380       390       400       410       420
inputs GCGACGGCGCGCCCGGGGCTCCGGGAGAGAAAGGCGAGGGCGGGAGGCCGGGACTGCCGGGACCTCGAGG
                         ::: ::.::..:::  :.:... : .:::          .::   .::::
       ------------------CTCAGGAAGGAAAA--CAAAAAAGTAAGG---------ACC---TCCTC----
                           210        220        230

              430       440       450       460       470       480       490
inputs GGACCCCGGGCCGCGAGGAGAGGCGGGACCCGCGGGGCCCACCGGGCCTGCCGGGGAGTGCTCGGTGCCT
                 :: : ::::.
       ----------CCTCTAGGAA--------------------------------------------------
                240

              500       510       520       530       540       550       560
inputs CCGCGATCCGCCTTCAGCGCCAAGCGCTCCGAGAGCCGGGTGCCTCCGCCGTCTGACGCACCCTTGCCCT
                                    :.:.:. :.   : :::                        ...:: .
```

FIG. 7A

```
       ------------------------------CAAAAAACATTTTCCT------------------AAACCAA
                                     250       260                      270

                570       580       590       600       610       620       630
inputs TCGACCGCGTGCTGGTGAACGAGCAGGGACATTACGACGCCGTCACCGGCAAGTTCACCTGCCAGGTGCC
       ::.. :          .:::  :.:::..:::  ::: .  :: :::         .:: ::.  :...:
       TCAGTC--------ATGA--GGGCAAAGAC--TACTTTTCCTTCA--------ATC-CCA--CTAAT---
                     280         290          300                 310

                640       650       660       670       680       690       700
inputs TGGGGTCTACTACTTCGCCGTCCATGCCACCGTCTACCGGGCCAGCCTGCAGTTTGATCTGGTGAAGAAT
       :.:..          :.::.:::                                 ::: ::           :
       TAGAA----------CACCATCC--------------------------------TTTTAT-----------T
        320                                                   330

                710       720       730       740       750       760       770
inputs GGCGAATCCATTGCCTCTTTCTTCCAGTTTTTCGGGGGGTGGCCCAAGCCAGCCTCGCTCTCGGGGGGGG
       : :.:..: .:     .:: .::: ::.:                  :..:
       GTCAATACTGT----ACTGACTTTCAAT-----------------CTTG----------------------
        340             350       360

                780       790       800       810       820       830       840
inputs CCATGGTGAGGCTGGAGCCTGAGGACCAAGTGTGGGTGCAGGTGGGTGTGGGTGACTACATTGGCATCTA
         ::...::.: :  :::::::..::              : .:..:.:
       --ATAAAGAAGAT--AGCCTGAAAAC--------------GTAGAATAT----------------------
            370        380                         390

                850       860       870       880       890       900       910
inputs TGCCAGCATCAAGACAGACAGCACCTTCTCCGGATTTCTGGTGTACTCCGACTGGCACAGCTCCCCAGTC
       : ::::::..:.                      :::. :..:                   .::::::::.::
       TTCCAGCTACT-----------------TCCATAAAT---------------------TGCTCCCCTGT-
         400                        410                                420

                920       930       940       950       960       970       980
inputs TTTGCTTAGTGCCCACTGCAAAGTGAGCTCATGCTCTCACTCCTAGAAGGAGGGTGTGAGGCTGACAACC
                                                                     ::.:::..
       -------------------------------------------------------------GCAGACGT--
                                                                       430

                990      1000      1010      1020      1030      1040      1050
inputs TGGTCATCCAGGAGGGCTGGCCCCCCTGGAATATTGTGAATGACTAGGGAGGTGGGGTAGAGCACTCTCC
            :.::: ..    :::: : ::::::::                ::: ::..:.: .:::     :
       ------AACCATAT---CTGGTCTCCCTGGAA----------------GAGCTGAAGAATTGCATGAT--
              440           450                        460        470

               1060      1070      1080      1090      1100      1110      1120
inputs GTCCTGCTGCTGGCAAGGAATGGGAACAGTGGCTGTCTGCGATCAGGTCTGGCAGCATGGGGCAGTGGCT
              ::::.:::          : ..:: :::  :::: :: ::    :    :: ::: :: :: .::::
       -------TGCTAGCA--------GTTTCA-TGG---TCTG-GAGCA---C---CATCATTGG-CATAGGCT
               480             490               500                 510       520

               1130      1140      1150      1160      1170      1180      1190
```

FIG. 7B

```
inputs GGATTTCTGCCCAAGACCAGAGGAGTGTGCTGTGCTGGCAAGTGTAAGTCCCCCAGTTGCTCTGGTCCAG
       :...     ::::::::.           ::    :.   :..  ..:.::         :::: .:   .: :::
       GATA-------CCAAGACCT----------CTT--CATTCTTCANTGAG-------GTTG-AC--ATACAG
                  530                     540       550                     560

                1200      1210      1220      1230      1240      1250      1260
inputs GAGCCCACGGTGGGGTGCTCTCTTCCTGGTCCTCTGCTTCTCTGGATCCTCCCCACCCCCTCCTGCTCCT
        .:: ::           ::.:: ::.:  : : :.:.: : ...:.             :  .. .: :
       TGGCACAT----------TCACTGCCAG--CTTTTACATGTGAAAAA-------------TGAAAAACGT
           570                 580        590                     600

                1270      1280      1290      1300      1310      1320      1330
inputs GGGGCCGGCCCTTTTCTCAGAGATCACTCAATAAACCTAAGAACCCTCCAAAAAAAAAAAAAAAAAAAAG
       .: :::.     :::.:. .: ::   :.:::: :::          :::::. ..:.:. :::
       AGTGCCA------TTCACTTGG--CA---ATTAAATCTA---------CCAAAGCTGAGATCAAA------
      610            620            630                640       650

inputs GGCGGCCGC

       ---------
```

FIG. 7C

```
ALIGN calculates a global alignment of two sequences
 version 2.0uPlease cite: Myers and Miller, CABIOS (1989)
> mT253 n.a.                                        1263 aa vs.
> adipocyte n.a. (AI417523)                          653 aa
scoring matrix: pam120.mat, gap penalties: -12/-4
30.4% identity;        Global alignment score: -840

               10        20        30        40        50        60        70
inputs GTCGACCCACGCGTCCGCGCTGTGAAGCCAGCAAGGAGCAACCAGAAGCTAGGAGTCAGTCAGCAAGGAC
       :                   : :   .::::.: :.:..    ..  .. ::: ::  ::.::::: :
       TT------------------TTT------TGCATGTAACTT----TTTTATTGAGGCA--CAACAAGG-C
                                      10            20        30

               80        90       100       110       120       130       140
inputs AGGGGCTGCCTGCCTACAGACTACAAGAGAGGTTCCTGGAGTCTGAGCCTCCGGGGTCACCACCATGAGG
       :  :                ..:::          : ::::::                        :.:::::
       ATTG-------------TAACT----------TGCCTGGA-----------------------CTTGAGG
     40                                  50                                 60

              150       160       170       180       190       200       210
inputs CCACTTCTTGCCCTTCTGCTTCTGGGTCTGGTGTCAGGCTCTCCTCCTCTGGACGACAACAAGATCCCCA
       : .           ::.: ::          .::  ::            :::.:::. :: :
       CAG-----------TCAGTTT----------AGTAAG------------CTGAACGTTAATA---------
                      70                                 80        90

              220       230       240       250       260       270       280
inputs GCCTGTGTCCCGGGCAGCCCGGCCTTCCAGGCACACCAGGTCACCATGGCAGCCAAGGCCTGCCTGGCCG
         :.:: .    ::.          ::  . ::: :: .: .:        .::  ::  .:: :: ::.:: :
       --CAGTTA--AGGA----------TTAAGTGCAAACAATAT--------ACATTCACAGCTTGACTAGC-G
            100                   110                 120       130       140

              290       300       310       320       330       340       350
inputs TGACGGCCGTGATGGCCGCGACGGTGCACCCGGAGCTCCGGGAGAGAAAGGCGAGGGCGGGAGACCGGGA
       .:.: .:                             : :.: .  ....::. ::       :.:.. :   : .
       AGGCTAC---------------------------ATCACAATTTATAAAGTGC-----CAGATTA---GTG
                                           150       160            170

              360       370       380       390       400       410       420
inputs CTACCTGGCCCACGTGGGGAGCCCGGGCCGCGTGGAGAGGCAGGGCCCATGGGGGCTATCGGGCCTGCGG
       :::  :: :  .:.                ::  ::.. .  ::     ::. .::..        ::  ..:..
       CTAATTGTCATTCA----------------GCTTGATTTTTCA----CCTCAGGAA------GGAAAACAA
        180       190                          200           210            220

              430       440       450       460       470       480       490
inputs GGGAGTGCTCGGTACCCCCACGATCAGCCTTCAGTGCCAAGCGATCCGAGAGCCGGGTACCTCCGCCAGC
       ...:::.   .: ::: ::.:        :::          :.:: ::.: .:.:.: .   :.:::
       AAAAGTA---AGGACCTCCTC------CCT--------CTAG-GAACAAAAAAC-ATTTTCCTA-------
                 230            240                250        260

              500       510       520       530       540       550       560
inputs CGACACACCCCTACCTTTCGACCGTGTGCTGCTAAATGAGCAGGGCCATTACGACCCCACTACTGGCAAG
           .::::..::..  :.::.:  ::.::..  ..:.      ::.:   :.: ::::::: :    .::
```

FIG. 8A

```
           -----------AACCAATCAGTCATGAG-GGCAAAGACTACTTTTCCTT--CAATCCCACTAAT---TAG
                        270       280       290       300       310

                  570       580       590       600       610       620       630
inputs TTCACCTGCCAAGTGCCTGGCGTCTACTACTTTGCTGTGCACGCCACTGTCTACCGGGCCAGCTTGCAGT
       ..::::. ::.. :.   : :       .:..:.::::       ::::.::.
       AACACCATCCTTTTA--TTG---------TCAATACTGT-------ACTGACTT-----------------
     320       330                 340              350

                  640       650       660       670       680       690       700
inputs TTGATCTTGTCAAAAACGGGCAGTCCATCGCCTCTTTCTTCCAGTATTTGGGGGGTGGCCCAAGCCAGC
                                      ::..::::     ..:...:..:.:.:::
       -------------------------------TCAATCTT-----GATAAAGAAGATAGCC---------
                                         360            370

                  710       720       730       740       750       760       770
inputs CTCGCTCTCAGGGGGTGCGATGGTAAGGCTAGAACCTGAGGACCAGGTGTGGGTGCAGGTGGGCGTGGGT
                  :....::..:..     :: ..::.:      :         :.:
       -----------TGAAAACGTAGAA-----TATTTCCAG-----C---------TAC--------------
                 380       390            400

                  780       790       800       810       820       830       840
inputs GATTACATTGGCATCTATGCCAGCATCAAGACAGACAGTACCTTCTCTGGATTTCTCGTCTATTCTGACT
         :: :::... . ::    ::  :   :.. .:::::. .:::.: :::::    ::::  :        ::
       --TTCCATAAATTGCT---CC--C--CTGTGCAGACGTAACCATATCTGG---TCTC--C--------CT
          410       420            430       440          450

                  850       860       870       880       890       900       910
inputs GGCACAGCTCCCCAGTCTTCGCTTAAAACACAGTGAACCCGGAGCTGGCACTTGCTCCTCAGTGGAGGGT
       :: : ::::    ::. :: ::.:.:..                :::.::: :: :           : :::
       GGAAGAGCTGA--AGAATT-GCATGATT---------------GCTAGCAGTTTC-----------ATGGT
          460        470                          480       490

                  920       930       940       950       960       970       980
inputs GTGACACTAACCCGCGCAGCGCATACCAGGAGGGCTGGCCCCCTGGAATATTGTGAATGACTTAGGAAGA
                                 :.:::      :: ::         .: :.::.:.:::: .::
       --------------------------CTGGA------GCACC-----------ATCATTGGCATAGGCTGA
                                   500                        510       520

                  990      1000      1010      1020      1030      1040      1050
inputs GAGGGAGCCACTTCCAGTCCCACTGCTGGCAATGAATGGAGACAGGCTGTCTGAGGTCAAGACAGCGTGG
                  :.:::.  ::.:: :.  :..             ::.      :::::: .::::
       -----------TACCAAGACCTCTTCATTCTT-----------CAN-------TGAGGT--TGACA------
                       530       540                          550

                 1060      1070      1080      1090      1100      1110      1120
inputs AGCAGTGGCTGGGTTTCTGCCCAGGACTTTAGAATGCAGTAGGCTGGCAGCTGTGGGTCCTGGCCCAGGA
       ..:::::::. . : .:::::  ..::::    :.::                ::::...  ::.   :..:
       TACAGTGGCACATTCACTGCC---AGCTTT----TACA--------------TGTGAAAAATGA---AAAA
     560       570           580                          590        600

                 1130      1140      1150      1160      1170      1180      1190
```

FIG. 8B

```
inputs CTCCAAGGTGGGATGCTCCATTCCTAGTCCTGTGTCCCCTCTAGGTCCCTGACTCCATCTCTGCTGCTCC
       :   ...:::        ::::::                 .::.::         : ::   :. . :: :
       C---GTAGTG-------CCATTC----------------ACTTGG---------CAAT---TAAATCTAC
           610                                620                 630

                1200      1210      1220      1230      1240      1250      1260
inputs CAGGGCAGGCCTTTTTCTCAGAGGTCACTTAATAAACCTAAAATCCTCAAAAAAAAAAAAAAAAGGGCGGC
       ::..::.:            :::                       :::::
       CAAAGCTG------------AGA-----------------------TCAAA--------------------
       640                                           650

inputs CGC
```

FIG. 8C

```
GTCGACCCACGCGTCCGCGGACGCGTGGGTGAGGGGAAGAGGCTGACTGTACGTTCCTTCTACTCTGGCACCACTCTCC       79

             M   G   P   S   T   P   L   L   I   L   F   L   L   S   W   S   G         17
AGGCTGCC    ATG GGG CCC AGC ACC CCT CTC CTC ATC TTG TTC CTT TTG TCA TGG TCG GGA       138

 P   L   Q   G   Q   Q   H   H   L   V   E   Y   M   E   R   R   L   A   A   L       37
CCC CTC CAA GGA CAG CAG CAC CAC CTT GTG GAG TAC ATG GAA CGC CGA CTA GCT GCT TTA      198

 E   E   R   L   A   Q   C   Q   D   Q   S   S   R   H   A   A   E   L   R   D       57
GAG GAA CGG CTG GCC CAG TGC CAG GAC CAG AGT AGT CGG CAT GCT GCT GAG CTG CGG GAC      258

 F   K   N   K   M   L   P   L   L   E   V   A   E   K   E   R   E   A   L   R       77
TTC AAG AAC AAG ATG CTG CCA CTG CTG GAG GTG GCA GAG AAG GAG CGG GAG GCA CTC AGA      318

 T   E   A   D   T   I   S   G   R   V   D   R   L   E   R   E   V   D   Y   L       97
ACT GAG GCC GAC ACC ATC TCC GGG AGA GTG GAT CGT CTG GAG CGG GAG GTA GAC TAT CTG      378

 E   T   Q   N   P   A   L   P   C   V   E   F   D   E   K   V   T   G   G   P      117
GAG ACC CAG AAC CCA GCT CTG CCC TGT GTA GAG TTT GAT GAG AAG GTG ACT GGA GGC CCT      438

 G   T   K   G   K   G   R   R   N   E   K   Y   D   M   V   T   D   C   G   Y      137
GGG ACC AAA GGC AAG GGA AGA AGG AAT GAG AAG TAC GAT ATG GTG ACA GAC TGT GGC TAC      498

 T   I   S   Q   V   R   S   M   K   I   L   K   R   F   G   G   P   A   G   L      157
ACA ATC TCT CAA GTG AGA TCA ATG AAG ATT CTG AAG CGA TTT GGT GGC CCA GCT GGT CTA      558

 W   T   K   D   P   L   G   Q   T   E   K   I   Y   V   L   D   G   T   Q   N      177
TGG ACC AAG GAT CCA CTG GGG CAA ACA GAG AAG ATC TAC GTG TTA GAT GGG ACA CAG AAT      618

 D   T   A   F   V   F   P   R   L   R   D   F   T   L   A   M   A   A   R   K      197
GAC ACA GCC TTT GTC TTC CCA AGG CTG CGT GAC TTC ACC CTT GCC ATG GCT GCC CGG AAA      678

 A   S   R   V   R   V   P   F   P   W   V   G   T   G   Q   L   V   Y   G   G      217
GCT TCC CGA GTC CGG GTG CCC TTC CCC TGG GTA GGC ACA GGG CAG CTG GTA TAT GGT GGC      738

 F   L   Y   F   A   R   R   P   P   G   R   P   G   G   G   G   E   M   E   N      237
TTT CTT TAT TTT GCT CGG AGG CCT CCT GGA AGA CCT GGT GGA GGT GGT GAG ATG GAG AAC      798

 T   L   Q   L   I   K   F   H   L   A   N   R   T   V   V   D   S   S   V   F      257
ACT TTG CAG CTA ATC AAA TTC CAC CTG GCA AAC CGA ACA GTG GTG GAC AGC TCA GTA TTC      858

 P   A   E   G   L   I   P   P   Y   G   L   T   A   D   T   Y   I   D   L   A      277
CCA GCA GAG GGG CTG ATC CCC CCC TAC GGC TTG ACA GCA GAC ACC TAC ATC GAC CTG GCA      918

 A   D   E   E   G   L   W   A   V   Y   A   T   R   E   D   D   R   H   L   C      297
GCT GAT GAG GAA GGT CTT TGG GCT GTC TAT GCC ACC CGG GAG GAT GAC AGG CAC TTG TGT      978

 L   A   K   L   D   P   Q   T   L   D   T   E   Q   Q   W   D   T   P   C   P      317
```

FIG. 9A

CTG GCC AAG TTA GAT CCA CAG ACA CTG GAC ACA GAG CAG CAG TGG GAC ACA CCA TGT CCC 1038

R E N A E A A F V I C G T L Y V V Y N T 337
AGA GAG AAT GCT GAG GCT GCC TTT GTC ATC TGT GGG ACC CTC TAT GTC GTC TAT AAC ACC 1098

R P A S R A R I Q C S F D A S G T L T P 357
CGT CCT GCC AGT CGG GCC CGC ATC CAG TGC TCC TTT GAT GCC AGC GGC ACC CTG ACC CCT 1158

E R A A L P Y F P R R Y G A H A S L R Y 377
GAA CGG GCA GCA CTC CCT TAT TTT CCC CGC AGA TAT GGT GCC CAT GCC AGC CTC CGC TAT 1218

N P R E R Q L Y A W D D G Y Q I V Y K L 397
AAC CCC CGA GAA CGC CAG CTC TAT GCC TGG GAT GAT GGC TAC CAG ATT GTC TAT AAG CTG 1278

E M R K K E E E V * 407
GAG ATG AGG AAG AAA GAG GAG GAG GTT TGA 1308

GGAGCTAGCCTTGTTTTTTGCATCTTTCTCACTCCCATACATTTATATTATATCCCCACTAAATTTCTTGTTCCTCATT 1387

CTTCAAATGTGGGCCAGTTGTGGCTCAAATCCTCTATATTTTTAGCCAATGGCAATCAAATTCTTTCAGCTCCTTTGTT 1466

TCATACGGAACTCCAGATCCTGAGTAATCCTTTTAGAGCCCGAAGAGTCAAAACCCTCAATGTTCCCTCCTGCTCTCCT 1545

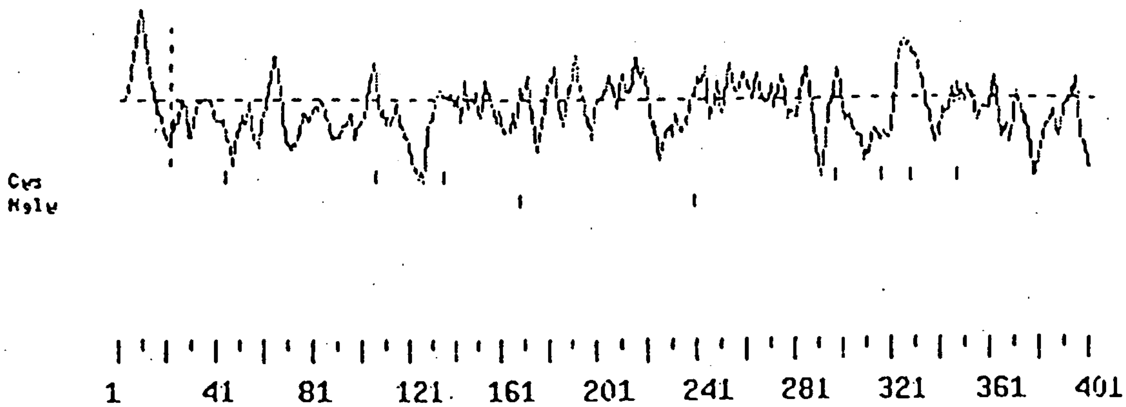
GCCCCATGTCAACAAATTTCAGGCTAAGGATGCCCCAGACCCAGGGCTCTAACCTTGTATGCGGGCAGGCCCAGGGAGC 1624

AGGCAGCAGTGTTCTTCCCCTCAGAGTGACTTGGGGAGGGAGAAATAGGAGGAGACGTCCAGCTCTGTCCTCTCTTCCT 1703

CACTCCTCCCTTCAGTGTCCTGAGGAACAGGACTTTCTCCACATTGTTTTGTATTGCAACATTTTGCATTAAAAGGAAA 1782

ATCCACTGCTAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAGGGCGGCCGC 1831

FIG. 9B



MGPSTPLLILFLLSWSGPLQGQQHHLVEYMERRLAALEERLAQCQDQSSRHAAELRDFKN
KMLPLLEVAEKEREALRTEADTISGRVDRLEREVDYLETQNPALPCVEFDEKVTGGPGTK
GKGRRNEKYDMVTDCGYTISQVRSMKILKRFGGPAGLWTKDPLGQTEKIYVLDGTQNDTA
FVFPRLRDFTLAMAARKASRVRVPFPWVGTGQLVYGGFLYFARRPPGRPGGGGEMENTLQ
LIKFHLANRTVVDSSVFPAEGLIPPYGLTADTYIDLAADEEGLWAVYATREDDRHLCLAK
LDPQTLDTEQQWDTPCPRENAEAAFVICGTLYVVYNTRPASRARIQCSFDASGTLTPERA
ALPYFPRRYGAHASLRYNPRERQLYAWDDGYQIVYKLEMRKKEEEV

FIG. 10

M G P S A P L L L L F F 12
GTCGACCCACGCGTCCGACTTAAGGCTGCC ATG GGG CCC AGT GCT CCT CTG CTG CTC CTC TTC TTT 66

L S W T G P L Q G Q Q H H L V E Y M E R 32
TTG TCA TGG ACG GGA CCC CTT CAG GGA CAG CAG CAC CAC CTT GTG GAG TAC ATG GAA CGC 126

R L A A L E E R L A Q C Q D Q S S R H A 52
CGA CTA GCT GCC TTA GAG GAA CGG CTG GCC CAA TGC CAG GAT CAG AGT AGT CGG CAT GCT 186

A E L R D F K N K M L P L L E V A E K E 72
GCC GAG CTT CGG GAC TTC AAA AAC AAG ATG TTG CCT CTC CTG GAG GTG GCA GAG AAG GAG 246

R E T L R T E A D S I S G R V D R L E R 92
CGG GAG ACC CTC AGA ACT GAA GCA GAC TCC ATC TCA GGA AGA GTG GAC CGT CTT GAA AGG 306

E V D Y L E T Q N P A L P C V E L D E K 112
GAG GTA GAC TAT CTG GAG ACA CAG AAC CCA GCT TTG CCC TGT GTA GAG CTG GAT GAG AAG 366

V T G G P G A K G K G R R N E K Y D M V 132
GTG ACT GGA GGT CCT GGA GCC AAA GGC AAG GGC CGA AGA AAT GAG AAA TAC GAT ATG GTG 426

T D C S Y T V A Q V R S M K I L K R F G 152
ACG GAC TGT AGC TAC ACA GTC GCT CAG GTG AGG TCA ATG AAG ATC CTG AAG CGG TTT GGT 486

G S V G L W T K D P L G P A E K I Y V L 172
GGT TCA GTT GGC CTA TGG ACC AAG GAT CCG CTG GGG CCA GCA GAG AAG ATC TAC GTG TTA 546

D G T Q N D T A F V F P R L R D F T L A 192
GAC GGC ACC CAG AAC GAC ACG GCT TTT GTC TTC CCA AGG CTG CGT GAC TTC ACC CTT GCC 606

M A A R K A S R I R V P F P W V G T G Q 212
ATG GCT GCC CGG AAA GCT TCC CGA ATT CGG GTG CCC TTC CCC TGG GTA GGC ACG GGG CAG 666

L V Y G G F L Y Y A R R P P G G P G G G 232
CTG GTG TAC GGT GGC TTC CTT TAT TAT GCT CGA AGG CCT CCT GGA GGA CCT GGA GGG GGT 726

G E L E N T L Q L I K F H L A N R T V V 252
GGT GAA TTG GAG AAC ACT CTG CAG CTG ATC AAA TTT CAC TTG GCA AAC CGA ACA GTG GTG 786

D S S V F P A E S L I P P Y G L T A D T 272
GAT AGC TCA GTG TTC CCT GCA GAG AGC CTG ATA CCC CCC TAC GGC CTG ACA GCA GAT ACA 846

Y I D L A A D E E G L W A V Y A T R D D 292
TAT ATC GAC CTG GCA GCT GAT GAG GAG GGC CTG TGG GCT GTC TAT GCC ACT CGA GAT GAT 906

D R H L C L A K L D P Q T L D T E Q Q W 312
GAC AGG CAT TTG TGT CTA GCC AAG TTA GAC CCA CAG ACA CTT GAC ACA GAG CAG CAG TGG 966

D T P C P R E N A E A A F V I C G T L Y 332

FIG. 11A

GAC ACA CCA TGT CCC AGA GAG AAC GCA GAG GCT GCG TTT GTC ATC TGT GGG ACC CTG TAC 1026

V V Y N T R P A S R A R I Q C S F D A S 352
GTT GTC TAT AAC ACC CGC CCT GCC AGT AGG GCT CGT ATT CAG TGT TCC TTC GAT GCC AGT 1086

G T L A P E R A A L S Y F P R R Y G A H 372
GGT ACT CTC GCC CCT GAA AGG GCA GCA CTC TCC TAT TTT CCA CGC CGA TAT GGT GCC CAT 1146

A S L R Y N P R E R Q L Y A W D D G Y Q 392
GCC AGC CTT CGC TAT AAC CCC CGT GAG CGC CAG CTG TAT GCC TGG GAT GAT GGC TAC CAG 1206

I V Y K L E M K K K E E E V * 407
ATT GTC TAC AAA TTG GAG ATG AAG AAG AAG GAG GAG GAA GTT TAA 1251

GCAGCTAGCCTTGTGCTCTTGATTCTTATGCCCAGACATTTATATTCCTGTGAGCTCTCCTGCAGTTCATCCTTCAAAA 1330

CGAAGGCCAGTGGTGGTAGCTCATATACCCTAATTTCTAAAGGACAACCAAATTCTCAAGCCCCTCTGTTTTATGCAGA 1409

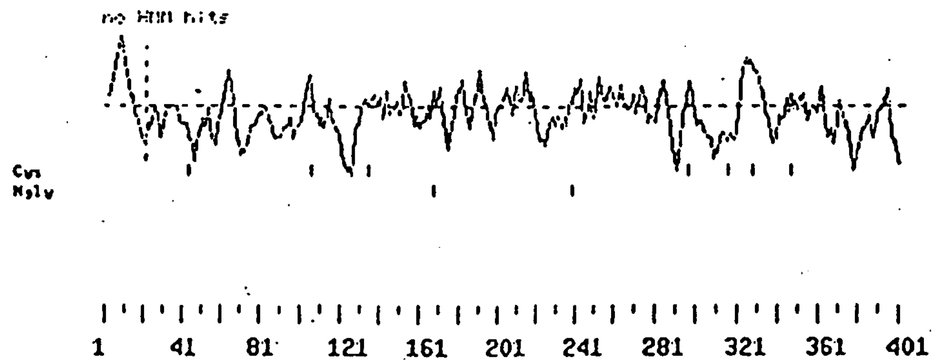
ACTCCAGATCCTGGGTAGCATTTTAGAACTGAACAGCAAACAAACACCCTAAATCTTCACTCCTGCCTTATGTCCACAA 1488

AGTTTAGTTCCAAACTCAGAGCCCTGTCCTTTGGAGAGGGTCAACCCCAGACAGCAGGCGACAGCATTCTTGCCCTCAG 1567

TATGACCGAAGGGAGAGAACTCAGAGACAAAGCTGCCCTCCCTCCCTTCCCCCTCCAGTGTAGGGGAGAATGGGGCTTT 1646

CCCCACATCACTTTGTATGGTAACAGTTTGCATTAAAAGGAAAACCCACCAAAAAAAAAAAAAAAAGGGCGGCCGC 1721

FIG. 11B



>mT257
MGPSAPLLLLFFLSWTGPLQGQQHHLVEYMERRLAALEERLAQCQDQSSRHAAELRDFKN
KMLPLLEVAEKERETLRTEADSISGRVDRLEREVDYLETQNPALPCVELDEKVTGGPGAK
GKGRRNEKYDMVTDCSYTVAQVRSMKILKRFGGSVGLWTKDPLGPAEKIYVLDGTQNDTA
FVFPRLRDFTLAMAARKASRIRVPFPWVGTGQLVYGGFLYYARRPPGGPGGGGELENTLQ
LIKFHLANRTVVDSSVFPAESLIPPYGLTADTYIDLAADEEGLWAVYATRDDDRHLCLAK
LDPQTLDTEQQWDTPCPRENAEAAFVICGTLYVVYNTRPASRARIQCSFDASGTLAPERA
ALSYFPRRYGAHASLRYNPRERQLYAWDDGYQIVYKLEMKKKEEEV

FIG. 12

```
ALIGN calculates a global alignment of two sequences
 version 2.0uPlease cite: Myers and Miller, CABIOS (1989)
> hT257 a.a.                                         406 aa vs.
> mT257a.a.                                          406 aa
scoring matrix: pam120.mat, gap penalties: -12/-4
94.1% identity;              Global alignment score: 2097

               10        20        30        40        50        60        70
inputs MGPSTPLLILFLLSWSGPLQGQQHHLVEYHERRLAALEERLAQCQDQSSRHAAELRDFKNKMLPLLEVAE
       ::::.:::.::.:::.::::::::::::::::::::::::::::::::::::::::::::::::::::::
       MGPSAPLLLLFFLSWTGPLQGQQHHLVEYHERRLAALEERLAQCQDQSSRHAAELRDFKNKMLPLLEVAE
               10        20        30        40        50        60        70

               80        90       100       110       120       130       140
inputs KEREALRTEADTISGRVDRLEREVDYLETQNPALPCVEFDEKVTGGPGTKGKGRRNEKYDMVTDCGYTIS
       ::::.:::::.::::::::::::::::::::::::::::.:::::::::.::::::::::::::::.:..
       KERETLRTEADSISGRVDRLEREVDYLETQNPALPCVELDEKVTGGPGAKGKGRRNEKYDMVTDCSYTVA
               80        90       100       110       120       130       140

              150       160       170       180       190       200       210
inputs QVRSMKILKRFGGPAGLWTKDPLGQTEKIYVLDGTQNDTAFVFPRLRDFTLAMAARKASRVRVPFPWVGT
       :::::::::::::..:::::::::..::::::::::::::::::::::::::::::::::.:::::::::
       QVRSMKILKRFGGSVGLWTKDPLGPAEKIYVLDGTQNDTAFVFPRLRDFTLAMAARKASRIRVPFPWVGT
              150       160       170       180       190       200       210

              220       230       240       250       260       270       280
inputs GQLVYGGFLYFARRPPGRPGGGGEMENTLQLIKFHLANRTVVDSSVFPAEGLIPPYGLTADTYIDLAADE
       ::::::::::.:::::: ::::::.::::::::::::::::::::::::::.::::::::::::::::::
       GQLVYGGFLYYARRPPGGPGGGGELENTLQLIKFHLANRTVVDSSVFPAESLIPPYGLTADTYIDLAADE
              220       230       240       250       260       270       280

              290       300       310       320       330       340       350
inputs EGLWAVYATREDDRHLCLAKLDPQTLDTEQQWDTPCPRENAEAAFVICGTLYVVYNTRPASRARIQCSFD
       ::::::::::.:::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
       EGLWAVYATRDDDRHLCLAKLDPQTLDTEQQWDTPCPRENAEAAFVICGTLYVVYNTRPASRARIQCSFD
              290       300       310       320       330       340       350

              360       370       380       390       400
inputs ASGTLTPERAALPYFPRRYGAHASLRYNPRERQLYAWDDGYQIVYKLEMRKKEEEV
       :::::.::::::.::::::::::::::::::::::::::::::::::::.::::::
       ASGTLAPERAALSYFPRRYGAHASLRYNPRERQLYAWDDGYQIVYKLEMKKKEEEV
              360       370       380       390       400
```

FIG. 13

```
ALIGN calculates a global alignment of two sequences
 version 2.0uPlease cite: Myers and Miller, CABIOS (1989)
> hT257 a.a.                                         406 aa vs.
> Patent Protein W75120 - (untitled)                 355 aa
scoring matrix: pam120.mat, gap penalties: -12/-4
86.9% identity;                 Global alignment score: 1681

               10        20        30        40        50        60        70
inputs MGPSTPLLILFLLSWSGPLQGQQHHLVEYMERRLAALEERLAQCQDQSSRHAAELRDFKNKMLPLLEVAE
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
       MGPSTPLLILFLLSWSGPLQGQQHHLVEYMERRLAALEERLAQCQDQSSRHAAELRDFKNKMLPLLEVAE
               10        20        30        40        50        60        70

               80        90       100       110       120       130       140
inputs KEREALRTEADTISGRVDRLEREVDYLETQNPALPCVEFDEKVTGGPGTKGKGRRNEKYDMVTDCGYTIS
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
       KEREALRTEADTISGRVDRLEREVDYLETQNPALPCVEFDEKVTGGPGTKGKGRRNEKYDMVTDCGYTIS
               80        90       100       110       120       130       140

              150       160       170       180       190       200       210
inputs QVRSMKILKRFGGPAGLWTKDPLGQTEKIYVLDGTQNDTAFVFPRLRDFTLAMAARKASRVRVPFPWVGT
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
       QVRSMKILKRFGGPAGLWTKDPLGQTEKIYVLDGTQNDTAFVFPRLRDFTLAMAARKASRVRVPFPWVGT
              150       160       170       180       190       200       210

              220       230       240       250       260       270       280
inputs GQLVYGGFLYFARRPPGRPGGGGEMENTLQLIKFHLANRTVVDSSVFPAEGLIPPYGLTADTYIDLAADE
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
       GQLVYGGFLYFARRPPGRPGGGGEMENTLQLIKFHLANRTVVDSSVFPAEGLIPPYGLTADTYIDLAADE
              220       230       240       250       260       270       280

              290       300       310       320       330       340       350
inputs EGLWAVYATREDDRHLCLAKLDPQTLDTEQQWDTPCPRENAEAAFVICGTLYVVYNTRPASRARIQCSFD
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
       EGLWAVYATREDDRHLCLAKLDPQTLDTEQQWDTPCPRENAEAAFVICGTLYVVYNTRPASRARIQCSFD
              290       300       310       320       330       340       350

              360       370       380       390       400
inputs ASGTLTPERAALPYFPRRYGAHASLRYNPRERQLYAWDDGYQIVYKLEMRKKEEEV
       ::: .
       ASGPX-----------------------------------------
```

FIG. 14

```
ALIGN calculates a global alignment of two sequences
 version 2.0uPlease cite: Myers and Miller, CABIOS (1989)
> T257 p a.                                  1832 aa vs.
> ac02146                                    1925 aa
scoring matrix: pam120.mat, gap penalties: -12/-4
93.5% identity;     Global alignment score: 9158

                10        20        30        40        50        60
inputs GTCGACCCACGCGTCC---GCGGACGCGTGGG--TGAGGGGAAGAGGCTGACTGTACGTTCCTTCTACTC
            ::: ::: :::   ::  .:: :  :::  :::::::::::.::::::::::::::::::::::::
       -----CCC-CGCCTCCAAAGCTAACCCTCGGGCTTGAGGGGAAGANGCTGACTGTACGTTCCTTCTACTC
                    10        20        30        40        50        60

          70        80        90       100       110       120       130
inputs TGGCACCACTCTCCAGGCTGCCATGGGGCCCAGCACCCCTCTCCTCATCTTGTTCCTTTTGTCATGGTCG
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
       TGGCACCACTCTCCAGGCTGCCATGGGGCCCAGCACCCCTCTCCTCATCTTGTTCCTTTTGTCATGGTCG
          70        80        90       100       110       120       130

         140       150       160       170       180       190       200
inputs GGACCCCTCCAAGGACAGCAGCACCACCTTGTGGAGTACATGGAACGCCGACTAGCTGCTTTAGAGGAAC
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
       GGACCCCTCCAAGGACAGCAGCACCACCTTGTGGAGTACATGGAACGCCGACTAGCTGCTTTAGAGGAAC
         140       150       160       170       180       190       200

         210       220       230       240       250       260       270
inputs GGCTGGCCCAGTGCCAGGACCAGAGTAGTCGGCATGCTGCTGAGCTGCGGGACTTCAAGAACAAGATGCT
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
       GGCTGGCCCAGTGCCAGGACCAGAGTAGTCGGCATGCTGCTGAGCTGCGGGACTTCAAGAACAAGATGCT
         210       220       230       240       250       260       270

         280       290       300       310       320       330       340
inputs -GCCACTGCTGGAGGTGGCAGAGAAGGAGCGGGAGGCACTCAGAACTGAGGCCGACACCATCTCCGGGAG
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
       NGCCACTGCTGGAGGTGGCAGAGAAGGAGCGGGAGGCACTCAGAACTGAGGCCGACACCATCTCCGGGAG
         280       290       300       310       320       330       340

         350       360       370       380       390       400       410
inputs AGTGGATCGTCTGGAGCGGGAGGTAGACTATCTGGAGACCCAGAACCCAGCTCTGCCCTGTGTAGAGTTT
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
       AGTGGATCGTCTGGAGCGGGAGGTAGACTATCTGGAGACCCAGAACCCAGCTCTGCCCTGTGTAGAGTTT
         350       360       370       380       390       400       410

         420       430       440       450       460       470       480
inputs GATGAGAAGGTGACTGGAGGCCCTGGGACCAAAGGCAAGGGAAGAAGGAATGAGAAGTACGATATGGTGA
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
       GATGAGAAGGTGACTGGAGGCCCTGGGACCAAAGGCAAGGGAAGAAGGAATGAGAAGTACGATATGGTGA
         420       430       440       450       460       470       480

         490       500       510       520       530       540       550
```

FIG. 15A

```
inputs CAGACTGTGGCTACACAATCTCTCAAGTGAGATCAATGAAGATTCTGAAGCGATTTGGTGGCCCAGCTGG
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
       CAGACTGTGGCTACACAATCTCTCAAGTGAGATCAATGAAGATTCTGAAGCGATTTGGTGGCCCAGCTGG
         490       500       510       520       530       540       550

         560       570       580       590       600       610       620
inputs TCTATGGACCAAGGATCCACTGGGGCAAACAGAGAAGATCTACGTGTTAGATGGGACACAGAATGACACA
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
       TCTATGGACCAAGGATCCACTGGGGCAAACAGAGAAGATCTACGTGTTAGATGGGACACAGAATGACACA
         560       570       580       590       600       610       620

         630       640       650       660       670       680       690
inputs GCCTTTGTCTTCCCAAGGCTGCGTGACTTCACCCTTGCCATGGCTGCCCGGAAAGCTTCCCGAGTCCGGG
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
       GCCTTTGTCTTCCCAAGGCTGCGTGACTTCACCCTTGCCATGGCTGCCCGGAAAGCTTCCCGAGTCCGGG
         630       640       650       660       670       680       690

         700       710       720       730       740       750       760
inputs TGCCCTTCCCCTGGGTAGGCACAGGGCAGCTGGTATATGGTGGCTTTCTTTATTTTGCTCGGAGGCCTCC
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
       TGCCCTTCCCCTGGGTAGGCACAGGGCAGCTGGTATATGGTGGCTTTCTTTATTTTGCTCGGAGGCCTCC
         700       710       720       730       740       750       760

         770       780       790       800       810       820       830
inputs TGGAAGACCTGGTGGAGGTGGTGAGATGGAGAACACTTTGCAGCTAATCAAATTCCACCTGGCAAACCGA
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
       TGGAAGACCTGGTGGAGGTGGTGAGATGGAGAACACTTTGCAGCTAATCAAATTCCACCTGGCAAACCGA
         770       780       790       800       810       820       830

         840       850       860       870       880       890       900
inputs ACAGTGGTGGACAGCTCAGTATTCCCAGCAGAGGGGCTGATCCCCCCCTACGGCTTGACAGCAGACACCT
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
       ACAGTGGTGGACAGCTCAGTATTCCCAGCAGAGGGGCTGATCCCCCCCTACGGCTTGACAGCAGACACCT
         840       850       860       870       880       890       900

         910       920       930       940       950       960       970
inputs ACATCGACCTGGCAGCTGATGAGGAAGGTCTTTGGGCTGTCTATGCCACCCGGGAGGATGACAGGCACTT
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
       ACATCGACCTGGCAGCTGATGAGGAAGGTCTTTGGGCTGTCTATGCCACCCGGGAGGATGACAGGCACTT
         910       920       930       940       950       960       970

         980       990      1000      1010      1020      1030      1040
inputs GTGTCTGGCCAAGTTAGATCCACAGACACTGGACACAGAGCAGCAGTGGGACACACCATGTCCCAGAGAG
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
       GTGTCTGGCCAAGTTAGATCCACAGACACTGGACACAGAGCAGCAGTGGGACACACCATGTCCCAGAGAG
         980       990      1000      1010      1020      1030      1040

        1050      1060      1070      1080      1090      1100      1110
inputs AATGCTGAGGCTGCCTTTGTCATCTGTGGGACCCTCTATGTCGTCTATAACACCCGTCCTGCCAGTCGGG
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
```

FIG. 15B

```
       AATGCTGAGGCTGCCTTTNTCATCTGTGGGACCCTCTATGTCGTCTATAACACCCGTCCTGCCAGTCGGG
          1050      1060      1070      1080      1090      1100      1110  -

          1120      1130      1140      1150      1160      1170      1180
inputs CCCGCATCCAGTGCTCCTTTGATGCCAGCGGCACCCTGACCCCTGAACGGCAGCACTCCCTTATTTCC
       ::::::::::::::::::::::::::::::: :::::::::::::::::::::::::::::::::::::
       CCCGCATCCAGTGCTCCTTTGATGCCAGCGG-ACCCTGACCCCTGAACGGCAGCACTCCCTTATTTCC
          1120      1130      1140      1150      1160      1170      1180

          1190      1200      1210      1220      1230      1240      1250
inputs CCGCAGATATGGTGCCCATGCCAGCCTCCGCTATAACCCCCGAGAACGCCAGCTCTATGCCTGGGATGAT
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
       CCGCAGATATGGTGCCCATGCCAGCCTCCGCTATAACCCCCGAGAACGCCAGCTCTATGCCTGGGATGAT
          1190      1200      1210      1220      1230      1240      1250

          1260      1270      1280      1290      1300      1310      1320
inputs GGCTACCAGATTGTCTATAAGCTGGAGATGAGGAAGAAAGAGGAGGAGGTTTGAGGAGCTAGCCTTGTTT
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
       CGCTACCAGATTGTCTATAAGCTGGAGATGAGGAAGAAAGAGGAGGAGGTTTGAGGAGCTAGCCTTGTTT
          1260      1270      1280      1290      1300      1310      1320

          1330      1340      1350      1360      1370      1380      1390
inputs TTTGCATCTTTCTCACTCCCATACATTTATATTATATCCCCACTAAATTTCTTGTTCCTCATTCTTCAAA
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
       TTTGCATCTTTCTCACTCCCATACATTTATATTATATCCCCACTAAATTTCTTGTTCCTCATTCTTCAAA
          1330      1340      1350      1360      1370      1380      1390

          1400      1410      1420      1430      1440      1450      1460
inputs TGTGGGCCAGTTGTGGCTCAAATCCTCTATATTTTTAGCCAATGGCAATCAAATTCTTTCAGCTCCTTTG
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
       TGTGGGCCAGTTGTGGCTCAAATCCTCTATATTTTTAGCCAATGGCAATCAAATTCTTTCAGCTCCTTTG
          1400      1410      1420      1430      1440      1450      1460

          1470      1480      1490      1500      1510      1520      1530
inputs TTTCATACGGAACTCCAGATCCTGAGTAATCCTTTTAGAGCCCGAAGAGTCAAAACCCTCAATGTTCCCT
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
       TTTCATACGGAACTCCAGATCCTGAGTAATCCTTTTAGAGCCCGAAGAGTCAAAACCCTCAATGTTCCCT
          1470      1480      1490      1500      1510      1520      1530

          1540      1550      1560      1570      1580      1590      1600
inputs CCTGCTCTCCTGCCCCATGTCAACAAATTTCAGGCTAAGGATGCCCCCAGACCCAGGGCTCTAACCTTGT
       ::::::::::::::::::::::::::::::::::::::::::::::: ::::::::::::::::::::::
       CCTGCTCTCCTGCCCCATGTCAACAAATTTCAGGCTAAGGATGCCCC-AGACCCAGGGCTCTAACCTTGT
          1540      1550      1560      1570      1580       1590      1600

          1610      1620      1630      1640      1650      1660      1670
inputs ATGCGGGCAGGCCCAGGGAGCAGGCAGCAGTGTTCTTCCCCTCAGAGTGACTTGGGGAGGGAGAAATAGG
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
       ATGCGGGCAGGCCCAGGGAGCAGGCAGCAGTGTTCTTCCCCTCAGAGTGACTTGGGGAGGGAGAAATAGG
          1610      1620      1630      1640      1650      1660      1670
```

FIG. 15C

```
          1680      1690      1700      1710      1720      1730      1740
inputs AGGAGACGTCCAGCTCTGTCCTCTCTTCCTCACTCCTCCCTTCAGTGTCCTGAGGAACAGGACTTTCTCC
       ::::::::::::::::::::::::::::::::::::::::::::::::::: ::::::::::::::::::
       AGGAGACGTCCAGCTCTGTCCTCTCTTCCTCACTCCTCCCTTCAGTGTCCTCAGGAACAGGACTTTCTCC
              1680      1690      1700      1710      1720      1730      1740

          1750      1760      1770      1780      1790      1800      1810
inputs ACATTGTTTTGTATTGCAACATTTTGCATTAAAAGGAAAATCCACTGCTAAAAAAAAAAAAAAAAAAAAA
       :::::::::::::::::::::::::::::::::::::::::::: .. .:::::::::::::::::::::
       ACATTGTTTTGTATTGCAACATTTTGCATTAAAAGGAAAATCCANAAAAAAAAAAAAAAAAAAAAAAAAA
              1750      1760      1770      1780      1790      1800      1810

          1820                                              1830
inputs AAAAAAAAGG-----------------------------------------GCGGCCGC-----------
       ::::::::..                                         ::::::::
       AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAACTGCGGCCGCTGTCCCTTCTG
              1820      1830      1840      1850      1860      1870      1880

inputs -------------------------------------------

       TCGTCTTCTCGCAGCCGTACCCTTCTGTCGTCTTCTCGCAGCC
              1890      1900      1910      1920
```

FIG. 15D

```
ALIGN calculates a global alignment of two sequences
 version 2.0uPlease cite: Myers and Miller, CABIOS (1989)
> mT257a.a.                                             406 aa vs.
> Patent Protein W75120 - (untitled)                    355 aa
scoring matrix: pam120.mat, gap penalties: -12/-4
81.8% identity;          Global alignment score: 1599

                10        20        30        40        50        60        70
inputs MGPSAPLLLLFFLSWTGPLQGQQHHLVEYMERRLAALEERLAQCQDQSSRHAAELRDFKNKMLPLLEVAE
       ::::.:::.::.::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
       MGPSTPLLILFLLSWSGPLQGQQHHLVEYMERRLAALEERLAQCQDQSSRHAAELRDFKNKMLPLLEVAE
                10        20        30        40        50        60        70

                80        90       100       110       120       130       140
inputs KERETLRTEADSISGRVDRLEREVDYLETQNPALPCVELDEKVTGGPGAKGKGRRNEKYDMVTDCSYTVA
       ::::.::::::.::::::::::::::::::::::::::.:::::::::.::::::::::::::::.::..
       KEREALRTEADTISGRVDRLEREVDYLETQNPALPCVEFDEKVTGGPGTKGKGRRNEKYDMVTDCGYTIS
                80        90       100       110       120       130       140

               150       160       170       180       190       200       210
inputs QVRSMKILKRFGGSVGLWTKDPLGPAEKIYVLDGTQNDTAFVFPRLRDFTLAMAARKASRIRVPFPWVGT
       :::::::::::::..:::::::::..::::::::::::::::::::::::::::::::::.:::::::::
       QVRSMKILKRFGGPAGLWTKDPLGQTEKIYVLDGTQNDTAFVFPRLRDFTLAMAARKASRVRVPFPWVGT
               150       160       170       180       190       200       210

               220       230       240       250       260       270       280
inputs GQLVYGGFLYYARRPPGGPGGGGELENTLQLIKFHLANRTVVDSSVFPAESLIPPYGLTADTYIDLAADE
       ::::::::::.:::::: :::::.::::::::::::::::::::::::::.:::::::::::::::::::
       GQLVYGGFLYFARRPPGRPGGGGEMENTLQLIKFHLANRTVVDSSVFPAEGLIPPYGLTADTYIDLAADE
               220       230       240       250       260       270       280

               290       300       310       320       330       340       350
nputs  EGLWAVYATRDDDRHLCLAKLDPQTLDTEQQWDTPCPRENAEAAFVICGTLYVVYNTRPASRARIQCSFD
       ::::::::::.:::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
       EGLWAVYATREDDRHLCLAKLDPQTLDTEQQWDTPCPRENAEAAFVICGTLYVVYNTRPASRARIQCSFD
               290       300       310       320       330       340       350

               360       370       380       390       400
nputs  ASGTLAPERAALSYFPRRYGAHASLRYNPRERQLYAWDDGYQIVYKLEMKKKEEEV
       ::: .
       ASGPX---------------------------------------------------
```

FIG. 16

```
ALIGN calculates a global alignment of two sequences
 version 2.0uPlease cite: Myers and Miller, CABIOS (1989)
> mT257 n.a.                                      1721 aa vs.
> Patent Nucleotide V34217 - (untitled)           1890 aa
scoring matrix: pam120.mat, gap penalties: -12/-4
76.2% identity;         Global alignment score: 6493

                             10                          20
inputs GT----------------CGACCCAC---GCGTCC--------------GACTTAAGG-----------
       :.                :: :::::   :: :::              :.:::.:::
       GAGCAGGAGAGAAGGCACCGCCCCACCCCGCCTCCAAAGCTAACCCTCGGGCTTGAGGGGAAGAGGCTGA
               10        20        30        40        50        60        70

                                                30        40        50
inputs ------------------------------------CTGCCATGGGGCCCAGTGCTCCTCTGCTGCTCCT
                                           ::::::::::::::: .: ::::: ::  :: :
       CTGTACGTTCCTTCTACTCTGGCACCACTCTCCAGGCTGCCATGGGGCCCAGCACCCCTCTCCTCATCTT
               80        90       100       110       120       130       140

     60        70        80        90       100       110       120
inputs CTTCTTTTTGTCATGGACGGGACCCCTTCAGGGACAGCAGCACCACCTTGTGGAGTACATGGAACGCCGA
        ::: :::::::::::.:::::::::: ::.::::::::::::::::::::::::::::::::::::::
       GTTCCTTTTGTCATGGTCGGGACCCCTCCAAGGACAGCAGCACCACCTTGTGGAGTACATGGAACGCCGA
              150       160       170       180       190       200       210

    130       140       150       160       170       180       190
inputs CTAGCTGCCTTAGAGGAACGGCTGGCCCAATGCCAGGATCAGAGTAGTCGGCATGCTGCCGAGCTTCGGG
       :::::::: ::::::::::::::::::::.:::::::: :::::::::::::::::::: ::::: ::::
       CTAGCTGCTTTAGAGGAACGGCTGGCCCAGTGCCAGGACCAGAGTAGTCGGCATGCTGCTGAGCTGCGGG
              220       230       240       250       260       270       280

    200       210       220       230       240       250       260
inputs ACTTCAAAAACAAGATGTTGCCTCTCCTGGAGGTGGCAGAGAAGGAGCGGGAGACCCTCAGAACTGAAGC
       ::::::::.:::::::: :::::.:: ::::::::::::::::::::::::::::.: ::::::::::.::
       ACTTCAAGAACAAGATGCTGCCACTGCTGGAGGTGGCAGAGAAGGAGCGGGAGGCACTCAGAACTGAGGC
              290       300       310       320       330       340       350

    270       280       290       300       310       320       330
inputs AGACTCCATCTCAGGAAGAGTGGACCGTCTTGAAAGGGAGGTAGACTATCTGGAGACACAGAACCCAGCT
        :::.:::::: ::.::::::::: ::::: ::. :::::::::::::::::::::: ::::::::::::
       CGACACCATCTCCGGGAGAGTGGATCGTCTGGAGCGGGAGGTAGACTATCTGGAGACCCAGAACCCAGCT
              360       370       380       390       400       410       420

    340       350       360       370       380       390       400
inputs TTGCCCTGTGTAGAGCTGGATGAGAAGGTGACTGGAGGTCCTGGAGCCAAAGGCAAGGGCCGAAGAAATG
       :::::::::::::: : :::::::::::::::::: ::::::..:::::::::::::::  ::::.::::
       CTGCCCTGTGTAGAGTTTGATGAGAAGGTGACTGGAGGCCCTGGGACCAAAGGCAAGGGAAGAAGGAATG
              430       440       450       460       470       480       490

    410       420       430       440       450       460       470
nputs AGAAATACGATATGGTGACGGACTGTAGCTACACAGTCGCTCAGGTGAGGTCAATGAAGATCCTGAAGCG
      ::::.:::::::::::::::.:::::::.:::::::::.:: ::::.:::::.::::::::::::: :::::::
      AGAAGTACGATATGGTGACAGACTGTGGCTACACAATCTCTCAAGTGAGATCAATGAAGATTCTGAAGCG
              500       510       520       530       540       550       560

    480       490       500       510       520       530       540
nputs GTTTGGTGGTTCAGTTGGCCTATGGACCAAGGATCCGCTGGGGCCAGCAGAGAAGATCTACGTGTTAGAC
      .::::::::  ::: ::: ::::::::::::::::::.::::::: :.:::::::::::::::::::::
      ATTTGGTGGCCCAGCTGGTCTATGGACCAAGGATCCACTGGGGCAAACAGAGAAGATCTACGTGTTAGAT
              570       580       590       600       610       620       630

    550       560       570       580       590       600       610
nputs GGCACCCAGAACGACACGGCTTTTGTCTTCCCAAGGCTGCGTGACTTCACCCTTGCCATGGCTGCCCGGA
      :: :: ::::: :::::.:: ::::::::::::::::::::::::::::::::::::::::::::::::::
      GGGACACAGAATGACACAGCCTTTGTCTTCCCAAGGCTGCGTGACTTCACCCTTGCCATGGCTGCCCGGA
              640       650       660       670       680       690       700

    620       630       640       650       660       670       680
iputs AAGCTTCCCGAATTCGGGTGCCCTTCCCCTGGGTAGGCACGGGGCAGCTGGTGTACGGTGGCTTCCTTTA
      :::::::::::.: ::::::::::::::::::::::::::.:::::::::::.:: :::::::: :::::
```

FIG. 17A

```
       AAGCTTCCCGAGTCCGGGTGCCCTTCCCCTGGGTAGGCACAGGGCAGCTGGTATATGGTGGCTTTCTTTA
              710       720       730       740       750       760       770

     690       700       710       720       730       740       750
inputs TTATGCTCGAAGGCCTCCTGGAGGACCTGGAGGGGGTGGTGAATTGGAGAACACTCTGCAGCTGATCAAA
       ::.:::::.:::::::::::::.::::::::.::.::::::::..::::::::::: ::::::::.:::::
       TTTTGCTCGGAGGCCTCCTGGAAGACCTGGTGGAGGTGGTGAGATGGAGAACACTTTGCAGCTAATCAAA
              780       790       800       810       820       830       840

     760       770       780       790       800       810       820
inputs TTTCACTTGGCAAACCGAACAGTGGTGGATAGCTCAGTGTTCCCTGCAGAGAGCCTGATACCCCCCTACG
       :: ::: ::::::::::::::::::::::: ::::::.:::.:.::::.:::::.: ::::: ::::::::::
       TTCCACCTGGCAAACCGAACAGTGGTGGACAGCTCAGTATTCCCAGCAGAGGGGCTGATCCCCCCCTACG
              850       860       870       880       890       900       910

     830       840       850       860       870       880       890
inputs GCCTGACAGCAGATACATATATCGACCTGGCAGCTGATGAGGAGGGCCTGTGGGCTGTCTATGCCACTCG
       :: :::::::::: :: :: :::::::::::::::::::::::.::: :: ::::::::::::::::: ::
       GCTTGACAGCAGACACCTACATCGACCTGGCAGCTGATGAGGAAGGTCTTTGGGCTGTCTATGCCACCCG
              920       930       940       950       960       970       980

     900       910       920       930       940       950       960
inputs AGATGATGACAGGCATTTGTGTCTAGCCAAGTTAGACCCACAGACACTTGACACAGAGCAGCAGTGGGAC
       .:: :::::::::::: :::::::.:::::::::::: ::::::::::: ::::::::::::::::::::::
       GGAGGATGACAGGCACTTGTGTCTGGCCAAGTTAGATCCACAGACACTGGACACAGAGCAGCAGTGGGAC
              990      1000      1010      1020      1030      1040      1050

     970       980       990      1000      1010      1020      1030
inputs ACACCATGTCCCAGAGAGAACGCAGAGGCTGCGTTTGTCATCTGTGGGACCCTGTACGTTGTCTATAACA
       ::::::::::::::::::: ::.::::::::: ::::::::::::::::::::: :: :: :::::::::
       ACACCATGTCCCAGAGAGAATGCTGAGGCTGCCTTTGTCATCTGTGGGACCCTCTATGTCGTCTATAACA
             1060      1070      1080      1090      1100      1110      1120

    1040      1050      1060      1070      1080      1090      1100
inputs CCCGCCCTGCCAGTAGGGCTCGTATTCAGTGTTCCTTCGATGCCAGTGGTACTCTCGCCCCTGAAAGGGC
       :::: ::::::::: :::: :: :: ::::: ::::: :::::::: :: :: :: .:::::::: ::::
       CCCGTCCTGCCAGTCGGGCCCGCATCCAGTGCTCCTTTGATGCCAGCGG-ACCCTGACCCCTGAACGGGC
             1130      1140      1150      1160      1170      1180

    1110      1120      1130      1140      1150      1160      1170
inputs AGCACTCTCCTATTTTCCACGCCGATATGGTGCCCATGCCAGCCTTCGCTATAACCCCCGTGAGCGCCAG
       ::::::: : :::::::: ::: :::::::::::::::::::::: :::::::::::::.::.::::::
       AGCACTCCCTTATTTTCCCCGCAGATATGGTGCCCATGCCAGCCTCCGCTATAACCCCCGAGAACGCCAG
    1190      1200      1210      1220      1230      1240      1250

    1180      1190      1200      1210      1220      1230      1240
inputs CTGTATGCCTGGGATGATGGCTACCAGATTGTCTACAAATTGGAGATGAAGAAGAAGGAGGAGGAAGTTT
       :: ::::::::::::::::::::::::::::::::: ::. :::::::::.::::::.:::::::::.::::
       CTCTATGCCTGGGATGATGGCTACCAGATTGTCTATAAGCTGGAGATGAGGAAGAAAGAGGAGGAGGTTT
    1260      1270      1280      1290      1300      1310      1320

    1250      1260        1270      1280      1290             1300      1310
inputs AAGCAGCTAGCCTTGTGCT---CTTGATTCTTATGCCCAGACATTTATATT-----CCTGTGAGCTCTCC
       .:: ::::::::::::  :     :.: .:::: :  :::: ::::::::::           :: .   :. : ::
       GAGGAGCTAGCCTTGTTTTTTGCATCTTTCTCACTCCCATACATTTATATTATATCCCCACTAAATTTCT
    1330      1340      1350      1360      1370      1380      1390

          1320      1330      1340      1350      1360      1370
inputs TGCAGTTCATCCTTCAAAACGAAGGCCAGTGGTGGTAGCTCATATACCCTAATTTCTAA----AGGACAA
       :: .  :::: :::::::. :..::::::: ::::    ::::.:: : :::..:: :.:      : :.:::
       TGTTCCTCATTCTTCAAAT-GTGGGCCAGTTGTGG---CTCAAATCCTCTATATTTTTAGCCAATGGCAA
    1400      1410      1420      1430      1440      1450      1460

    1380      1390      1400      1410      1420      1430      1440
inputs CCAAATTCTCA-AGCCCCTCTGTTTTATGCAGAACTCCAGATCCTGGGTAG-CATTTTAGAACTGAACAG
       :::::::: . ::: ::: ::::: ::.:.::::::::::::::::.:::. : ::::::.:   .: ::
       TCAAATTCTTTCAGCTCCTTTGTTTCATACGGAACTCCAGATCCTGAGTAATCCTTTTAGAGCCCGA-AG
          1470      1480      1490      1500      1510      1520      1530

          1450      1460      1470      1480      1490
```

FIG. 17B

```
inputs CAAACAAACACCCTAAAT------CTTCACTCCTGCCTTATGTCCACAAAGTT-------TAGTT---CC
        ..   :::: : :.:..:      :: :.::::::::  ::::: ::::: ::        ..:.:   ::
       AGTCAAAACCCTCAATGTTCCCTCCTGCTCTCCTGCCCCATGTCAACAAATTTCAGGCTAAGGATGCCCC
           1540      1550      1560      1570      1580      1590      1600

   1500      1510      1520      1530      1540      1550      1560
inputs AAACTCAGAGCCCTGTCCTTTGGAGAGGGTCAACCCCAGACAGCAGGCGACAGCATTCTTGCCCTCAGTA
       :.:: :::.:: ::..::::  ..: ::: ::. :::::. ::::::::..::: .::::: ::::::::..
       AGACCCAGGGCTCTAACCTTGTATGCGGG-CAGGCCCAGGGAGCAGGCAGCAGTGTTCTTCCCCTCAGAG
           1610      1620      1630      1640      1650      1660      1670

   1570      1580      1590             1600          1610      1620
inputs TGACC-GAAGGGAGAGAACTCAGAGA-------CAAAGCTGCCCTC----CCTCCCTTCCCCCTCCAGTG
       ::::  :..:.:.::::: : .:::.        ::.  ::: ::::     :::: :: : :::: :::::
       TGACTTGGGGAGGGAGAAATAGGAGGAGACGTCCAGCTCTGTCCTCTCTTCCTCACTCCTCCCTTCAGTG
            1680      1690      1700      1710      1720      1730      1740

     1630      1640      1650      1660      1670      1680      1690
inputs TAGGGGAGAATGGGGCTTTCCCCACATCACTTTGTATGGTAACAGTTTGCATTAAAAGGAAAACCCAC--
       :    :..::: .::.::::: :::::: . ::::::: : :::: ::::::::::::::::: ::::
       TCCTGAGGAACAGGACTTTCTCCACATTGTTTTGTATTGCAACATTTTGCATTAAAAGGAAAATCCACTG
            1750      1760      1770      1780      1790      1800      1810

        1700      1710                                                   1720
inputs CAAAAAAAAAAAAAAAAGGG---------------CGGC------------------------------CG
       :::::::::::::::::...                ::::                               :.
       CAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAACGGCACGAGGGGGGGTCCCGTACCCAATNGCCCTCA
            1820      1830      1840      1850      1860      1870      1880

inputs C------
       :
       CATGCAT
           1890
```

FIG. 17C

GTCGACCCACGCGTNCNTCCAGCGTNCGGAGCCGCCCTGGGTGTCAGCGGCTCGGCTCCCGCGCACGCTCCGGCCGTCG 79

M 1
CGCAGCCTCGGCACCTGCAGGTCCGTGCGTCCCGCGGCTGGCGCCCCTGACTCCGTCCCGGCCAGGGAGGGCC ATG 155

I S L P G P L V T N L X R F L F L G L S 21
ATT TCC CTC CCG GGG CCC CTG GTG ACC AAC TTG NTG CGG TTT TTG TTC CTG GGG CTG AGT 215

A L A P P S R A Q L Q L H L P A N R L Q 41
GCC CTC GCG CCC CCC TCG CGG GCC CAG CTG CAA CTG CAC TTG CCC GCC AAC CGG TTG CAG 275

A V E E G E S G A S A W Y T L H R E V S 61
GCG GTG GAG GAG GGG GAA AGT GGT GCT TCA GCA TGG TAC ACC TTG CAC AGG GAG GTG TCT 335

S S Q P W E V P F V M W F F K Q K E K E 81
TCA TCC CAG CCA TGG GAG GTG CCC TTT GTG ATG TGG TTC TTC AAA CAG AAA GAA AAG GAG 395

D Q V L S Y I N G V T T S K P G V S L V 101
GAT CAG GTG TTG TCC TAC ATC AAT GGG GTC ACA ACA AGC AAA CCT GGA GTA TCC TTG GTC 455

Y S M P S R N L S L R V E G L Q E K D S 121
TAC TCC ATG CCC TCC CGG AAC CTG TCC CTG CGG GTG GAG GGT CTC CAG GAG AAA GAC TCT 515

G P Y S C S V N V Q D K Q G K S R G H S 141
GGC CCC TAC AGC TGC TCC GTG AAT GTG CAA GAC AAA CAA GGC AAA TCT AGG GGC CAC AGC 575

I K T L E L N V L V P P A P P S C R L Q 161
ATC AAA ACC TTA GAA CTC AAT GTA CTG GTT CCT CCA GCT CCT CCA TCC TGC CGT CTC CAG 635

G V P H V G A N V T L S C Q S P R S K P 181
GGT GTG CCC CAT GTG GGG GCA AAC GTG ACC CTG AGC TGC CAG TCT CCA AGG AGT AAG CCC 695

A V Q Y Q W D R Q L P S F Q T F F A P A 201
GCT GTC CAA TAC CAG TGG GAT CGG CAG CTT CCA TCC TTC CAG ACT TTC TTT GCA CCA GCA 755

L D V I R G S L S L T N L S S S M A G V 221
TTA GAT GTC ATC CGT GGG TCT TTA AGC CTC ACC AAC CTT TCG TCT TCC ATG GCT GGA GTC 815

Y V C K A H N E V G T A Q C N V T L E V 241
TAT GTC TGC AAG GCC CAC AAT GAG GTG GGC ACT GCC CAA TGT AAT GTG ACG CTG GAA GTG 875

S T G P G A A V V A E A V V G T L V G L 261
AGC ACA GGG CCT GGA GCT GCA GTG GTT GCT GAA GCT GTT GTG GGT ACC CTG GTT GGA CTG 935

G L L A G L V L L Y H R R G K A L E E P 281
GGG TTG CTG GCT GGG CTG GTC CTC TTG TAC CAC CGC CGG GGC AAG GCC CTG GAG GAG CCA 995

A N D I K E D A I A P R T L P W P K S S 301

FIG. 18A

GCC AAT GAT ATC AAG GAG GAT GCC ATT GCT CCC CGG ACC CTG CCC TGG CCC AAG AGC TCA 1055

D T I S K N G T L S S V T S A R A L R —P 321
GAC ACA ATC TCC AAG AAT GGG ACC CTT TCC TCT GTC ACC TCC GCA CGA GCC CTC CGG CCA 1115

P H G P P R P G A L T P T P S L S S Q A 341
CCC CAT GGC CCT CCC AGG CCT GGT GCA TTG ACC CCC ACG CCC AGT CTA TCC AGC CAG GCC 1175

L P S P R H A H D R W G P P S T N I P H 361
CTG CCC TCA CCA AGA CAT GCC CAC GAC AGA TGG GGC CCA CCC TCA ACC AAT ATC CCC CAT 1235

P W W G F F L W L * 371
CCC TGG TGG GGT TTT TTC CTT TGG CTT TGA 1265

GCCGCATGGGTGCTGNGCCTGTGATGGNGCCTGCCCAGAGTCAAGCTGGCTCTCTGGTATGATGACCCCACCACTCATT 1344

GGCTAAAGGATTTGGGGTCTCTCCTTCCTATAAGGGTCACCTCTAGCACAGAGGCCTGAGTCATGGGAAAGAGTCACAC 1423

TCCTGACCCTTAGTACTCTGCCCCCACCTCTCTTTACTGTGGGAAAACCATCTCAGTAAGACCTAAGTGTCCAGGAGAC 1502

AGAAGGAGAAGAGGAAGTGGATCTGGAATTGGGAGGAGCCTCCACCCACCCCTGACTCCTCCTTATGAAGCCAGCTGCT 1581

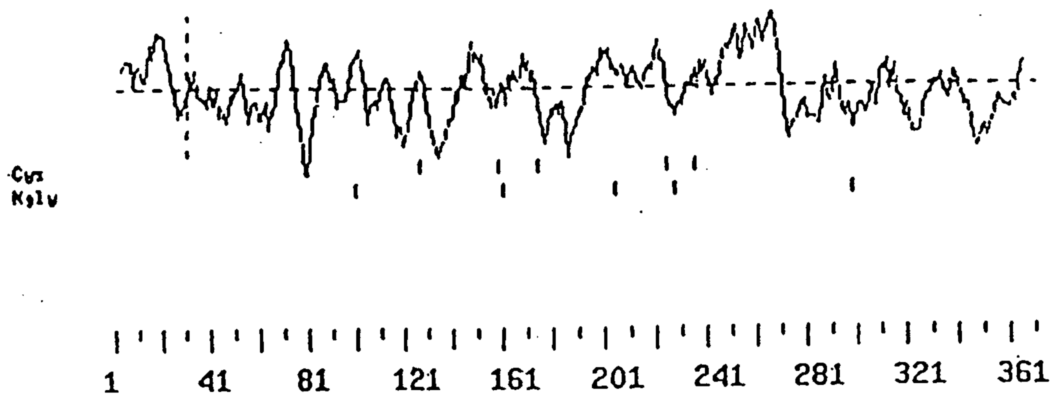
GAAATTAGCTACTCACCAAGAGTGAGGGGCAGAGACTTCCAGTCACTGAGTCTCCCAGGCCCCCTTGATCTGTACCCCA 1660

CCCCTATCTAACACCACCCTTGGCTCCCACTCCAGCTCCCTGTATTGATATAACCTGTCAGGCTGGCTTGGTTAGGTTT 1739

TACTGGGGCAGAGGATAGGGAATCTCTTATTAAAACTAACATGAAATATGTGTTGTTTTCATTTGCAAATTTAAATAAA 1818

GATACATAATGTTTGTATGAGATAAGAAAAAAAAAAAAAAAGGGCGGCCGC 1869

FIG. 18B



MISLPGPLVTNLXRFLFLGLSALAPPSRAQLQLHLPANRLQAVEEGESGASAWYTLHREV
SSSQPWEVPFVMWFFKQKEKEDQVLSYINGVTTSKPGVSLVYSMPSRNLSLRVEGLQEKD
SGPYSCSVNVQDKQGKSRGHSIKTLELNVLVPPAPPSCRLQGVPHVGANVTLSCQSPRSK
PAVQYQWDRQLPSFQTFFAPALDVIRGSLSLTNLSSSMAGVYVCKAHNEVGTAQCNVTLE
VSTGPGAAVVAEAVVGTLVGLGLLAGLVLLYHRRGKALEEPANDIKEDAIAPRTLPWPKS
SDTISKNGTLSSVTSARALRPPHGPPRPGALTPTPSLSSQALPSPRHAHDRWGPPSTNIP
HPWWGFFLWL

FIG. 19

```
GTCGACCCACGCGTCCGGTGCACATTCGGGTTGCCGCCGCTCACCCACAACACCTGTAGACACCGTGTGTCCAACTCTC   79

                            M   I   L   Q   A   G   T   P   E   T   S   L   L      13
CCTGAGTACTCCGGGCCAAGGAGGGCC ATG ATT CTT CAG GCT GGA ACC CCC GAG ACC AGC TTG CTG   145

R   V   L   F   L   G   L   S   T   L   A   A   F   S   R   A   Q   M   E   L      33
CGG GTT TTG TTC CTG GGA CTG AGT ACC CTT GCT GCC TTC TCC CGA GCT CAG ATG GAG TTG   205

H   V   P   P   G   L   N   K   L   E   A   V   E   G   E   E   V   V   L   P      53
CAC GTG CCC CCG GGC CTC AAC AAA TTG GAA GCG GTA GAG GGA GAA GAA GTG GTG CTC CCC   265

A   W   Y   T   M   A   R   E   E   S   W   S   H   P   R   E   V   P   I   L      73
GCC TGG TAC ACG ATG GCA CGG GAG GAG TCG TGG TCC CAC CCC CGG GAG GTG CCC ATC CTG   325

I   W   F   L   E   Q   E   G   K   E   P   N   Q   V   L   S   Y   I   N   G      93
ATC TGG TTC TTG GAA CAA GAA GGG AAG GAA CCA AAC CAG GTG TTG TCT TAC ATT AAT GGA   385

V   M   T   N   K   P   G   T   A   L   V   H   S   I   S   S   R   N   V   S     113
GTC ATG ACA AAT AAA CCT GGA ACA GCC CTG GTC CAC TCT ATC TCT TCA CGG AAT GTG TCC   445

L   R   L   G   A   L   Q   E   G   D   S   G   T   Y   R   C   S   V   N   V     133
CTG CGC CTG GGG GCA CTC CAG GAG GGA GAC TCT GGG ACT TAC CGC TGT TCT GTC AAT GTG   505

Q   N   D   E   G   K   S   I   G   H   S   I   K   S   I   E   L   K   V   L     153
CAG AAT GAT GAA GGC AAA AGT ATA GGC CAC AGC ATC AAA AGC ATA GAG CTC AAA GTG CTG   565

V   P   P   A   P   P   S   C   S   L   Q   G   V   P   Y   V   G   T   N   V     173
GTT CCT CCA GCT CCT CCA TCC TGT AGT TTA CAG GGT GTA CCC TAT GTC GGG ACC AAT GTG   625

T   L   N   C   K   S   P   R   S   K   P   T   A   Q   Y   Q   W   E   R   L     193
ACC CTG AAC TGC AAG TCC CCA AGG AGT AAA CCT ACT GCT CAG TAC CAG TGG GAG AGG CTG   685

A   P   S   S   Q   V   F   F   G   P   A   L   D   A   V   R   G   S   L   K     213
GCC CCA TCC TCC CAG GTC TTC TTT GGA CCA GCC TTA GAT GCT GTT CGT GGA TCT TTA AAG   745

L   T   N   L   S   I   A   M   S   G   V   Y   V   C   K   A   Q   N   R   V     233
CTC ACT AAC CTT TCC ATT GCC ATG TCT GGA GTC TAT GTC TGC AAG GCT CAA AAC AGA GTG   805

G   F   A   K   C   N   V   T   L   D   V   M   T   G   S   K   A   A   V   V     253
GGC TTT GCC AAG TGC AAC GTG ACC TTG GAC GTG ATG ACA GGG TCC AAG GCT GCA GTG GTC   865

A   G   A   V   V   G   T   F   V   G   L   V   L   I   A   G   L   V   L   L     273
GCT GGA GCA GTT GTG GGC ACT TTT GTT GGG TTG GTG CTG ATA GCT GGG CTG GTC CTG TTG   925

Y   Q   R   R   S   K   T   L   E   E   L   A   N   D   I   K   E   D   A   I     293
TAC CAG CGC CGG AGC AAG ACC TTG GAA GAG CTG GCC AAT GAT ATC AAG GAA GAT GCC ATT   985

A   P   R   T   L   P   W   T   K   G   S   D   T   I   S   K   N   G   T   L     313
GCT CCC CGG ACC TTG CCT TGG ACC AAA GGC TCA GAC ACA ATC TCC AAG AAT GGG ACA CTT  1045
```

FIG. 20A

S S V T S A R A L R P P K A A P P R P G 333
TCT TCG GTC ACC TCA GCA CGA GCT CTG CGG CCA CCC AAG GCT GCT CCT CCA AGA CCT GGC 1105

T F T P T P S V S S Q A L S S P R L P R 353
ACA TTT ACT CCC ACA CCC AGT GTC TCT AGC CAG GCC CTG TCC TCA CCA AGA CTG CCC AGG 1165

V D E P P P Q A V S L T P G G V S S S A 373
GTA GAT GAA CCC CCA CCT CAG GCA GTG TCC CTG ACC CCA GGT GGG GTT TCT TCT TCT GCT 1225

L S R M G A V P V M V P A Q S Q A G S L 393
CTG AGC CGC ATG GGT GCT GTG CCT GTG ATG GTG CCT GCA CAG AGT CAG GCT GGG TCT CTT 1285

V 395
GTG TGA 1291

TAGCCCAGGCACTCATTAGCTACATCTGGTATCTGACCTTTCTGTAAAGGTCTCCTTGTGGCACAGAGGACTCAATCTT 1370

GGGAGGATGCCCACATTCTAGACCTCCAGTCCTTTGCTCCTACCTCCTTCTATTGTTGGAATACTGGGCCTCAGTAAGA 1449

CTAAAATCTGGGTCAAAGGACAAAAGGAGGAAATGGACCTGAGGTAGGGGGTTGGGAGTGAGGAGGCTTCACTTCCTCC 1528

CTGCTTCTCCCTGAAGCCAGATGAATGCTGCGGAAGATCGGCTACCCTCCAAGGGCTCTGGAGGAGACTGCCAGTCAGT 1607

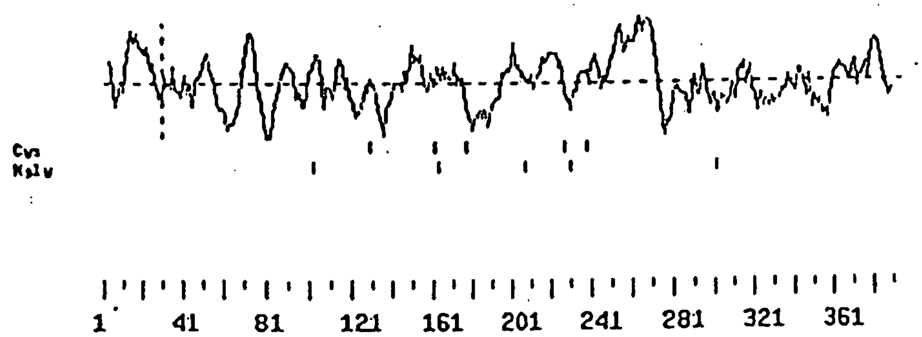
ATGCCCCTGGCTCTGTGATCTGTACAACACCCTTATCTAATGCTGTCCTTTGCCGTTCGCTCCATCTCCCTGTATTAA 1686

ATAACCTGTCCTGCTGGCTTGGCTGGGTTTTGTTGTAGCAGGGGGATAGGAAAGACATTTTAAAATCTGACTTGAAAT 1765

GATGTTTTTGTTTTTATTTTGCAAATTTCAATAAAGATACATCGCATTTGCATGGAAAAAAAAAAAAAAAAGGCGGCC 1844

1846

FIG. 20B



>mT258
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EESWSHPREVPILIWFLEQEGKEPNQVLSYINGVMTNKPGTALVHSISSRNVSLRLGALQ
EGDSGTYRCSVNVQNDEGKSIGHSIKSIELKVLVPPAPPSCSLQGVPYVGTNVTLNCKSP
RSKPTAQYQWERLAPSSQVFFGPALDAVRGSLKLTNLSIAMSGVYVCKAQNRVGFAKCNV
TLDVMTGSKAAVVAGAVVGTFVGLVLIAGLVLLYQRRSKTLEELANDIKEDAIAPRTLPW
TKGSDTISKNGTLSSVTSARALRPPKAAPPRPGTFTPTPSVSSQALSSPRLPRVDEPPPQ
AVSLTPGGVSSSALSRMGAVPVMVPAQSQAGSLV

FIG. 21

```
ALIGN calculates a global alignment of two sequences
 version 2.0uPlease cite: Myers and Miller, CABIOS (1989)
> hT258a.a.                                    370 aa vs.
> mT258 a.a.                                   394 aa
scoring matrix: pam120.mat, gap penalties: -12/-4
62.8% identity;             Global alignment score: 1085

                10        20        30        40        50        60
inputs MISLPGPLVTNLXRFLFLGLSALAPPSRAQLQLHLPA--NRLQAVEEGESGASAWYTLHREVSSSQPWEV
       ::  .:   :.:.: ::::::.::. ::::..::.:.  :.:.:::  :   .::::. :: : :.:.::
       MILQAGTPETSLLRVLFLGLSTLAAFSRAQMELHVPPGLNKLEAVEGEEVVLPAWYTMAREESWSHPREV
                10        20        30        40        50        60        70

       70        80        90       100       110       120       130
inputs PFVMWFFKQKEKE-DQVLSYINGVTTSKPGVSLVYSMPSRNLSLRVEGLQEKDSGPYSCSVNVQDKQGKS
       :...::. :  :: .:::::::::: :.:::..:: :..:::.:::. .::: ::: : ::::::. .:::
       PILIWFLEQEGKEPNQVLSYINGVMTNKPGTALVHSISSRNVSLRLGALQEGDSGTYRCSVNVQNDEGKS
                80        90       100       110       120       130       140

       140       150       160       170       180       190       200
inputs RGHSIKTLELNVLVPPAPPSCRLQGVPHVGANVTLSCQSPRSKPAVQYQWDRQLPSFQTFFAPALDVIRG
        :::::..::.:::::::::: ::::: ::.::::.:.::::::..::::.:  :: :.::.::::..::
       IGHSIKSIELKVLVPPAPPSCSLQGVPYVGTNVTLNCKSPRSKPTAQYQWERLAPSSQVFFGPALDAVRG
               150       160       170       180       190       200       210

       210       220       230       240       250       260       270
inputs SLSLTNLSSSMAGVYVCKAHNEVGTAQCNVTLEVSTGPGAAVVAEAVVGTLVGLGLLAGLVLLYHRRGKA
       :: ::::: .:.::::::.: :: :.:::::.: ::. ::::: :::::.::: :.::::::::.::.:.
       SLKLTNLSIAMSGVYVCKAQNRVGFAKCNVTLDVMTGSKAAVVAGAVVGTFVGLVLIAGLVLLYQRRSKT
               220       230       240       250       260       270       280

       280       290       300       310       320        330       340
inputs LEEPANDIKEDAIAPRTLPWPKSSDTISKNGTLSSVTSARALRPPHG-PPRPGALTPTPSLSSQALPSPR
       ::: ::::::::::::::::: :.:::::::::::::::::::::::: . ::::..:::::.:::::.:::
       LEELANDIKEDAIAPRTLPWTKGSDTISKNGTLSSVTSARALRPPKAAPPRPGTFTPTPSVSSQALSSPR
               29C       300       310       320       330       340       350

                                 350       360       370
inputs HAH---------------------DRWGPPSTNIPHPWWGFFLWL
        ..                   .: :. .. .: .  .  : .
       LPRVDEPPPQAVSLTPGGVSSSALSRMGAVPVMVPAQSQAGSL-V
               360       370       380       390
```

FIG. 22

```
ALIGN calculates a global alignment of two sequences
 version 2.0uPlease cite: Myers and Miller, CABIOS (1989)
> hT258a.a.                                        370 aa vs.
> SwissProt Q99795 - (untitled)                    319 aa
scoring matrix: pam120.mat, gap penalties: -12/-4
23.0% identity;          Global alignment score: -102

                10        20        30        40        50        60
inputs MISLPGPLVTNLXRFLFLGLSALAPPSRAQLQLHLPANRLQAVEEG-ESGASAWYTLHREVSSSQPWEVP
       :..   :.. .:.  . . ..:..  .  .. :. . . ..      ...:..  : .
       MVGKMWPVLWTLCA-VRVTVDAISVETPQDV-LRASQGKSVTLPCTYHTSTSSREGLIQWDKLLLTHTER
                10        20        30        40        50        60

      70        80        90       100       110       120       130
inputs FVMWFFKQKEKEDQVLSYINGVTTSKPGVSLVYSMPSRNLSLRVEGLQEKDSGPYSCSVNVQDKQGKSRG
        :.: : .:.       ::.:      :  ::.  .     . :. .. :    :.: : :::.. .     :
       VVIWPFSNKN-------YIHG-ELYKNRVSISNNAEQSDASITIDQLTMADNGTYECSVSLMSDLE---G
        70               80        90       100       110       120

     140       150       160       170       180        190       200
inputs HSIKTLELNVLVPPAPPSCRLQGVPHVGANVTLSCQSPRSKPAVQYQWDR--QLPSFQTFFAPALDVIRG
       ..    . : :::::. : :  ..:      .:.:. :.:::  . :. :: : :     :     :  .  :: .
       NTKSRVRLLVLVPPSKPECGIEGETIIGNNIQLTCQSKEGSPTPQYSWKRYNILNQEQPLAQPASGQ---
       130       140       150       160       170       180       190

       210       220       230       240       250       260       270
inputs SLSLTNLSSSMAGVYVVCKAHNEVGTAQCNVTLEVSTGP-GAAVVAEAVVGTLVGLGLLAGLVLLYHRRGK
       ..:: :.:.. .: :.: . :: ::   ::.:.: . . ..:. .   .::....: ... ..       :::
       PVSLKNISTDTSGYYICTSSNEEGTQFCNITVAVRSPSMNVALYVGIAVGVVAALIIIGIIIYCCCCRGK
          200       210       220       230       240       250       260

      280       290       300       310       320       330       340
inputs ALEEPANDIKEDAIAPRTLPWPKSSDTISKNGTLSSVTSARALRPPHGPPRPGALTPTPSLSSQALPSPR
        .. ..: ::::                             :. :  .   : :  :      .      .. . :
       --DDNTED-KEDA---------------------------RPNREAYEEP-PEQLRELSRERE-EE-DDYR
           270                                       280       290       300

       350       360       370
inputs HAHDRWGPPSTNIPHPWWGFFLWL
       .. .:  . . . . :.      :
       QEEQR--STGRESPDH-----LDQ
           310
```

FIG. 23

```
ALIGN calculates a global alignment of two sequences
 version 2.0uPlease cite: Myers and Miller, CABIOS (1989)
> hT258 n.a.                                       1869 aa vs.
> GenBank U79725 - Human A33 antigen precursor mR  2793 aa
scoring matrix: pam120.mat, gap penalties: -12/-4
40.6% identity;          Global alignment score: 1182

                             10             20
inputs GTCGACCC------------ACGCGTNCNT------CCAG----------------C------------
         : ::::            .:  :  .:.:      ::.:                :
       --CTACCCCTTTGTGAGCAGTCTAGGACTTTGTACACCTGTTAAGTAGGGAGAAGGCAGGGGAGGTGGCT
               10        20        30        40        50        60

                             30                                     40     50
inputs ----------GTNC----GGAG-------------CCGC------CCT-------GGGTGTCA-GCG-GC
                  :..:    :::.              :: :      :::       .:::::.:: . : ::
       GGTTTAAGGGGAACTTGAGGGAAGTAGGGAAGACTCCTCTTGGGACCTTTGGAGTAGGTGACACATGAGC
       70        80        90        100       110       120       130

              60          70            80            90
inputs TCGGCTCCCGCGCAC--GC---TCCGGCCGT----CGCGC-AGCCT---CGGCA----C----C------
        :.:: :: :: ::: ::   :::.:: :.    : :.: .:::.   :.::.    :    :
       CCAGCCCCAGCTCACCTGCCAATCCAGCTGAGGAGCTCACCTGCCAATCCAGCTGAGGCTGGGCAGAGGT
       140       150       160       170       180       190       200

                             100         110         120
inputs -------------------TGCAGG----TCC----GTGC--GTCCCG---CGGCTGGCGCC----CCTG
                           ::::::    :::    : ::  : :: :   : ::::  ::     ::.:
       GGGTGAGAAGAGGGAAAATTGCAGGGACCTCCAGTTGGGCCAGGCCAGAAGCTGCTGTAGCTTTAACCAG
       210       220       230       240       250       260       270

       130                   140                   150
inputs AC---TCCGTCC----------CGGCCAGGGA-------------GGGC----------------CATGA
       ::   :: :.::          : ::::: ::             ::::                ::::.
       ACAGCTCAGACCTGTCTGGAGGCTGCCAGTGACAGGTTAGGTTTAGGGCAGAGAAGAAGCAAGACCATGG
       280       290       300       310       320       330       340

                   160                 170       180
inputs TTT-----------CC-----------CTCCCGGGCC--CCTGGTGACCAAC-------------TTGN
       :             ::           :.: : : ::  :  :::::::..:             : :.
       TGGGGAAGATGTGGCCTGTGTTGTGGACACTCTGTGCAGTCAGGGTGACCGTCGATGCCATCTCTGTGGA
       350       360       370       380       390       400       410

       190            200                210         220
inputs TGC------GGTTTTTGTTC---------CTGGGGCTGAGTG---CCCT-C---GCGCC--CC--------
       ..:      ::.  :: :::         :.:::. .:::::   :::: :   ::.::  ::
       AACTCCGCAGGACGTTCTTCGGGCTTCGCAGGGAAAGAGTGTCACCCTGCCCTGCACCTACCACACTTCC
       420       430       440       450       460       470       480

       230                    240                 250                     260
inputs -CCTC-------GCGGGCC-----CA---------GCTGCAACT-GCACTTGC------------CCGCC
        ::::       : ::: :     ::         ::: :. :: .:.:.:.:            :   :
       ACCTCCAGTCGAGAGGGACTTATTCAATGGGATAAGCTCCTCCTCACTCATACGGAAAGGGTGGTCATCT
       490       500       510       520       530       540       550

           270       280                   290       300       310      320
inputs AACCGGTTGCAGGCGGTGG---------AGGAGGG---GGAAAGTGGTGCTTCAGCATGGTACACCTTGC
       ..:::  :: ::..:.....         .::.:.:   ..:::..  :: :::::::.    :: .:::
       GGCCGTTTTCAAACAAAAACTACATCCATGGTGAGCTTTATAAGAATCGCGTCAGCATATCCAACAATGC
       560       570       580       590       600       610       620

                 330      340                     350        360
inputs A---CAGGGAGGTGTCTTCATC-CCA-----------GCCATGGGAGG----TGC-CCTT--TGTGATGT
       .   :::    :.:: :: :::: :::           .:::::: .:.     :: :::.  .:::.: :
       TGAGCAGTCCGATGCCTCCATCACCATTGATCAGCTGACCATGGCTGACAACGGCACCTACGAGTGTTCT
       630       640       650       660       670       680       690

     370              380        390        400                 410
inputs GGTTCT------TCAAAC--AGAAAGAAAAGGAGGATCAGGTGT---------TGTCCT-----------
       :   ::       :::.:: .::..: ::, .  ...::: ::::          :::::
```

FIG. 24A

```
       GTCTCGCTGATGTCAGACCTGGAGGGCAACACCAAGTCACGTGTCCGCCTGTTGGTCCTCGTGCCACCCT
       700       710       720       730       740       750       760

                                                 420       430       440
inputs ---------------ACATCAA--------------TGGGGTCA-CAACAAGCAAACCTG--GAGTATC
                      .:::::.:.            ::::..:: ::.: :::..:::::  .:  :.
       CCAAACCAGAATGCGGCATCGAGGGAGAGACCATAATTGGGAACAACATCCAGCTGACCTGCCAATCAAA
       770       780       790       800       810       820       830

       450       460                                     470             480
inputs CTTGGTCTACTCCATGCCCTC------------------------CCGGAA------------CCTGTC
        .:: :: :.::::. :::::                         :: :::            :::: :
       GGAGGGCT-CACCAACCCCTCAGTACAGCTGGAAGAGGTACAACATCCTGAATCAGGAGCAGCCCCTGGC
       840       850       860       870       880       890       900

                   490       500       510          520
inputs CCTGC-------GGGT-GGAGGGTCTCC-AGGAGAAAGACTC---TGGCCC---------CTACAGCTG-
       ::.::       .::: .:     :::::: .:.::::...:::             ::::: :::
       CCAGCCAGCCTCAGGTCAGCCTGTCTCCCTGAAGAATATCTCCACAGACACATCGGGTTACTACATCTGT
       910       920       930       940       950       960       970

       530       540       550         560        570
inputs --CTCCGTGAATGTGCAAGACAAACAAG---GCAA-ATCTAGG-GGCCA-CAG---------CAT---CA
         ::::.  ::::.: :.:. : .::.   :::: :::. :: ::::. :::         :::    :.
       ACCTCCAGCAATGAGGAGGGGACGCAGTTCTGCAACATCACGGTGGCCGTCAGATCTCCCTCCATGAACG
       980       990       1000      1010      1020      1030      1040

       580           590       600            610         620
inputs AAACC---TTAG-----AACTCAATGTAC-TGGTT-----CCTC-----CA---GCTCCTCCATC--CTG
       ...::   :..:     :.: :..:: .: :::::     ::::     ::   ::. :. ::::  :::
       TGGCCCTGTATGTGGGCATCGCGGTGGGCGTGGTTGCAGCCCTCATTATCATTGGCATCATCATCTACTG
       1050      1060      1070      1080      1090      1100      1110

           630       640              650          660            670
inputs C--CGTCT-CCAGGGTGTG--C-----CCCATGTG----GGGGCAAACGTGACC---CTGAGCTGCCAGT
       :  :  :: ::..:: ..:  :      : :. ..:    ::.: :..:..:.::   : :.: .:::..:
       CTGCTGCTGCCGAGGGAAGGACGACAACACTGAAGACAAGGAGGATGCAAGGCCGAACCGGGAAGCCTAT
       1120      1130      1140      1150      1160      1170      1180

              680         690       700                          710
inputs -------CTCCAAGG-AG-TAAGCCCGCTGTCCAA-------------------TAC---CAGTGGG
              :.:::..:: :: ::::  .:: ::::.                     :::   ::. ..:
       GAGGAGCCACCAGAGCAGCTAAGAGAACTTTCCAGAGAGAGGGAGGAGGAGGATGACTACAGGCAAGAAG
       1190      1200      1210      1220      1230      1240      1250

             720          730           740         750          760
inputs ATCGG-----CA----GCTTCCATCC---TTCCAG-ACTTTCTTTG-CA--CCAGCATTAGATGTCATCC
       : :.:     ::    :: : ::::      .::: .: . :. :: ::  ::::::  ::: : :. :
       AGCAGAGGAGCACTGGGCGTGAATCCCCGGACCACCTCGACCAGTGACAGGCCAGCAGCAGAGGGCGGCG
       1260      1270      1280      1290      1300      1310      1320

       770            780         790            800       810          820
inputs GTGGG------------TCTTTAAGCCTCA-CCAA----CCTTTCGTCTTCCATGGCTGGAGTCTA-TGT
       :.::.            ::.:: . :: :. ::..    :: :::  ::: :...::  . :::  :::
       GAGGAAGGGTTAGGGGTTCATTCTCCCGCTTCCTGGCCTCCCTTCTCCTTTCTAAGCCCTGTTCTCCTGT
       1330      1340      1350      1360      1370      1380      1390

                830       840          850          860             870
inputs CTGCAAGGCCCA--CAATGAGGTGGGCA---CTGCCC-AATGTAA--TGTG----AC---GCTGG-----
       :       . ::::  ::.::: : ::.::   :: ::: :.::: :  ::::    ::   :::::
       CCCTCCATCCCAGACATTGATGGGGACATTTCTTCCCCAGTGTCAGCTGTGGGGAACATGGCTGGCCTGG
       1400      1410      1420      1430      1440      1450      1460

               880       890       900       910       920          930
inputs -AAGTGAG-CACAGGGCCTGGAGCTGCAGTGGTTGCTGAAGCTGTTGTGGGTACCCT---GGTTG-GACT
       .::: :.: : :.: :: ::.. :::.:.  : .:::.  :::: ..: .. ::::   :: :: :::.
       TAAGGGGGTCCCTGTGC-TGATCCTGCTGACCTCACTGTC-CTGTGAAGTAACCCCTCCTGGCTGTGACA
       1470      1480      1490      1500      1510      1520      1530

          940       950                 960       970                 980
```

FIG. 24B

```
inputs GGGGTTGCTGGCTGGGC--------TGGTCCT--CTTGTACCACCGC------CGG----GGCAAG-GC-
          : ::: ::: :::          ..:.::.  ::  ..::.::.:         ::    ::::.: ::
       CCTGGTGCGGGCCTGGCCCTCACTCAAGACCAGGCTGCAGCCTCCACTTCCCTCGTAGTTGGCAGGAGCT
         1540      1550      1560      1570      1580      1590      1600

             990                           1000      1010      1020
inputs CCTGGAGG---AGC-CAG---------------CCAAT--GATATC---AAGGAGG--ATGCCAT------
       :::::::.:  ::: :.:                ::: :   ::. ::   :.:::::  ::::::
       CCTGGAAGCACAGCGCTGAGCATGGGGCGCTCCCACTCAGAACTCTCCAGGGAGGCGATGCCAGCCTTGG
         1610      1620      1630      1640      1650      1660      1670

                           1030      1040      1050
inputs ----------------TGCTCCCCGGA---CCCTGC-CCTGG-----C-CCAAGAG---------CTCAG
                       ::::: :: :.   :::.:: :::::     : :::.:.:         :.:.
       GGGGTGGGGGCTGTCCTGCTCACCTGTGTGCCCAGCACCTGGAGGGGCACCAGGTGGAGGGTTTGCACTC
         1680      1690      1700      1710      1720      1730      1740

         1060      1070                                1080             1090
inputs -ACACAATCTCCAAGAATG-----------------------GGACCCT---TT-------CCTCTGT
        :::::.  : :..:::::                        ::.::::   ::       :::: .
       CACACATCTTTCTTGAATGAATGAAAGAATAAGTGAGTATGCTTGGGCCCTGCATTGGCCTGGCCTCCAG
         1750      1760      1770      1780      1790      1800      1810

                            1100      1110              .      1120
inputs CACC-------------TCCGCACGAGCC----CT-CCGG------CCA--CCC-C-----ATGGCC--C
       :.::             .:: ::: . ::    :: ::.:      :::  ::: :     :.::::  :
       CTCCCACTCCCTTTCCAACCTCACTTCCCGTAGCTGCCAGTATGTTCCAAACCCTCCTGGGAAGGCCACC
         1820      1830      1840      1850      1860      1870      1880

         1130      1140                          1150      1160      1170
inputs TCCCAGGCCTGGTGCATTGACCC--------------CCACGCCCAGTCTATC-CAGCCAGGC-------
       :::::  :::: :::: .:.:::              :::::.: :. :: ::: :.:::.: :
       TCCCACTCCTGCTGCACAGGCCCTGGGGAGCTTTTGCCCACACACTTTCCATCTCTGCCTGTCAATATCG
         1890      1900      1910      1920      1930      1940      1950

            1180      1190      1200      1210          1220      1230
inputs --CCTGCCCTCACCAAGACATGCCCACGACAGATGGGG--CCC--ACCCTCAACCAATATCCCCCATCCC
         :::: :: :.:::.: : . : :: ..:: :.::.    : :  ::::: . : :::.  :: ::: :
       TACCTGTCC-CTCCAGGCCCATCTCAAATCACAAGGATTTCTCTAACCCTATCCTAATTGTCCACATACG
         1960      1970      1980      1990      2000      2010      2020

      1240                1250      1260          1270            1280
inputs TGGTGG------GGTTT---TTTCCTTTGGCTT----TGAGCCGCATGG----GT--GCTGNGC------
       :::...      :::.   : ::: . : : .    ::.:::.::.::    ::   :::.::
       TGGAAACAATCCTGTTACTCTGTCCCACGTCCAATCATGGCCACAAGGCACAGTCTTCTGAGCGAGTGC
         2030      2040      2050      2060      2070      2080      2090

                 1290        1300      1310           1320       1330
inputs -----CTGTGATGGNGC--CTGC-CCA-GAGTCAAG--CTGGCTCTC-TGG--TATGATGACCC-----C
            ::::..:.:.::  :.:: ::. :.: ::.:  ::::  ::: :::  :.:: : .:::     :
       TCTCACTGTATTAGAGCGCCAGCTCCTTGGGGCAGGGCCTGGGCCTCATGGCTTTTGCTTTCCCTGAAGC
         2100      2110      2120      2130      2140      2150      2160

                 1340                1350        1360      1370      1380
inputs AC----------CACTCAT-----TGG---CTAAAG--GATTTGGGGTCTCTCCTTCCTATAAGGGT---
        :           :.: :::     :::   ::.:::  :.:::::::. .:: :::  ..:..  ::
       CCTAGTAGCTGGCGCCCATCCTAGTGGGCACTTAAGCTTAATTGGGGAAACTGCTTTGATTGGTTGTGCC
         2170      2180      2190      2200      2210      2220      2230

              1390           1400      1410      1420      1430
inputs --CAC--CTCTAG-CAC----AGA-GGCCTGAGTCATGGGAAAGAGTCACACTCCTGACCC-----TTAG
         : :  ::::.: :.:    ::: :. :  ::.:: .::.:.:: :: ::: ::..::::     :: .
       TTCCCTTCTCTGGTCTCCTTGAGATGATCGTAGACACAGGGATGATTCCCAC-CCAAACCCACGTATTCA
         2240      2250      2260      2270      2280      2290      2300

       1440      1450      1460      1470      1480      1490      1500
inputs TACTCTGCCCCCACCTCTCTTTACTGTGGGAAAACCA-TCTCAGTAAGACCTAAGTGTCCAGGAGACAGA
       :.:. ::      : :.:  .::. : :......: :: .:.::. ....: :.   :: :... .:.:.::
       TTCAGTGAGTTAAACACGAATTGATTTAAAGTGAACACACACAAGGGAGCTTGCTTG-CAGATGGTCTGA
         2310      2320      2330      2340      2350      2360      2370
```

FIG. 24C

```
              1510      1520                1530      1540      1550      1560
inputs AG----GAGAAGAGGAAGT--------GGATCTGGAATTGGGAGGAGCCTCCACCCACCCCTGACTCCTC
       .      :.:.  .::.:.:         .:. :.:.:...  :.  ..: ::::.:    :: :.  .     ::
       GTTCTTGTGTCCTGGTAATTCCTCTCCAGGCCAGAATAATTGGCATGTCTCCTCAACCCACATGGGGTTC
          2380      2390      2400      2410      2420      2430      2440

         1570      1580      1590      1600          1610      1620
inputs CTTATGAAGCCAGCTGCTGAAATTAGCTACTCA--CCAAG---AG---TGAGGGGCA-GAGACTTC----
       :: .: .. ::.::. :  .:..  :..: :.  :: .:   ::   . . ::::.  .:. :::
       CTGGTTGTTCCTGCATCCCGATACCTCAGCCCTGGCCCTGCCCAGCCCATTTGGGCTCTGGTTTTCTGGT
          2450      2460      2470      2480      2490      2500      2510

                 1630      1640                1650      1660      1670
inputs ----CAGTCACTGAGTC--TCCCA-GGCCCCCTT---------GATCTGTACCCCACCCCTATCTAACAC
           :.::: :::   :  ::::: .::: ::::          :: :. :.:  :. : ::.  .:.:.:
       GGGGCTGTC-CTGCTGCCCTCCCACAGCCTCCTTCTGTTTGTCGAGCATTTCTTCTACTCTTGAGAGCTC
          2520      2530      2540      2550      2560      2570      2580

          1680          1690      1700      1710      1720      1730
inputs ---CACCCTT--GGCTCCCA----CTCCAGCTCCCTGTATTGATATAACCTGTCAG--GCTGGCTTGGTT
          :: : :: :::: : .     ::: .: .::     . ::.: : ::: ..:.:  : : .::.
       AGGCAGCGTTAGGGCTGCTTAGGTCTCATGGACCAGTGGCTGGTCTCACCCAACTGCAGTTTACTATTGC
          2590      2600      2610      2620      2630      2640      2650

        1740      1750      1760           1770      1780      1790
inputs AGGTTTTACTGGG-GCAGAGGATAGGGAATC------TCTTATTAAAACTAAC-ATGAAATATGTGTTGT
       ..  ::.:.:::. : . ::.:.:. .:.::        :::..: . .:::.:. :: ...::....:::
       TATCTTTTCTGGATGATCAGAAAAATAATTCCATAAATCTATTGTCTACTTGCGATTTTTTAAAAAATGT
          2660      2670      2680      2690      2700      2710      2720

      1800      1810          1820      1830      1840      1850      1860
.nputs TTTCATTTGCAAATTTAAATAAAG---ATACATAATGTTTGTATGAGATAAGAAAAAAAAAAAAAAAGGG
       .:. .:::. :.::.:...::::     .:.:.: :: :   ..:::  :: ::.::.::.::::....:::
       ATATTTTTATATATATTGTTAAATCCTTTGCTTCAT-TCCAAATGCTTTCAGTAATAATAAAATTGTGGG
          2730      2740      2750      2760      2770      2780      2790

nputs CGGCCGC
       ::
      TGG----
```

FIG. 24D

```
ALIGN calculates a global alignment of two sequences
 version 2.0uPlease cite: Myers and Miller, CABIOS (1989)
> mT258 a.a.                                    394 aa vs.
> SwissProt Q99795 - (untitled)                 319 aa
scoring matrix: pam120.mat, gap penalties: -12/-4
23.0% identity;         Global alignment score: -149

               10        20        30        40        50        60        70
inputs MILQAGTPETSLLRVLFLGLSTLAAFSRAQMELHVPPGLNKLEAVEGEEVVLPAWYTMAREESWSHPREV
       :.          .  ::     :: :   .  .. :    . : : .: :.:: :  .    .  .
       MV-------GKMWPVLW----TLCAVRVTVDAISVETPQDVLRASQGKSVTLPCTYHTSTSSREGLIQWD
                        10            20        30        40        50

               80        90       100       110       120       130       140
inputs PILIWFLEQEGKEPNQVLSYINGVMTNKPGTALVHSISSRNVSLRLGALQEGDSGTYRCSVNVQNDEGKS
        .:.    :.    :     .::.: . ..  ... ..    ..:. .. :  .:.::: :::.. .:
       KLLLTHTERVVIWPFSNKNYIHGELYKNR-VSISNNAEQSDASITIDQLTMADNGTYECSVSLMSDLE--
     60        70        80        90       100       110       120

              150       160       170       180       190       200       210
inputs IGHSIKSIELKVLVPPAPPSCSLQGVPYVGTNVTLNCKSPRSKPTAQYQWERLAPSSQVFFGPALDAVRG
        :..   . : :::::. : :...:   .:.:. :.:.:  . ::.:: : : .   .:     :   ... :
       -GNTKSRVRLLVLVPPSKPECGIEGETIIGNNIQLTCQSKEGSPTPQYSWKRYNILNQE--QPLAQPASG
          130       140       150       160       170       180       190

               220       230       240       250       260       270
inputs -SLKLTNLSIAMSGVYVCKAQNRVGFAKCNVTLDVMTGS-KAAVVAGAVVGTFVGLVLIAGLVLLYQRRS
       .. : :.:.. :: :.: . :  :     ::.:.: . : ..:. .: .::. ..:.:.   ...:
       QPVSLKNISTDTSGYYICTSSNEEGTQFCNITVAVRSPSMNVALYVGIAVGVVAALIIIG--IIIYCCCC
          200       210       220       230       240       250       260

   280       290       300       310       320       330       340
inputs KTLEELANDIKEDAIAPRTLPWTKGSDTISKNGTLSSVTSARALRPPKAAPPRPGTFTPTPSVSSQALSS
       .  .. ..: ::::                         :. :  . ..:: .          ..::
       RGKDDNTED-KEDA--------------------------RPNREAYEEPPEQ---------LRELSR
            270                                   280                 290

   350       360       370       380       390
inputs PRLPRVDEPPPQAVSLTPGGVSSSALSRMGAVPVMVPAQSQAGSLV
       :     ..    :.   . :  :.. :..
       EREE--EDDYRQEEQRSTGRESPDHLDQ------------------
            300       310
```

FIG. 25

```
ALIGN calculates a global alignment of two sequences
 version 2.0uPlease cite: Myers and Miller, CABIOS (1989)
> mT258 n.a.                                    1846 aa vs.
> GenBank U79725 - Human A33 antigen precursor mR  2793 aa
scoring matrix: pam120.mat, gap penalties: -12/-4
40.0% identity;          Global alignment score: 908

                     10                 20                          30
inputs GTCGACCC------ACGC-GTC-----CG--GTGCAC--ATT-------------C--GGGTTGCCGCC
         : ::::      . :: :::     :   ::.:::  .::             :   :::. :  ::
       --CTACCCCTTTGTGAGCAGTCTAGGACTTTGTACACCTGTTAAGTAGGGAGAAGGCAGGGGAGGTGGCT
                  10        20        30        40        50        60

                  40                            50        60              70
inputs G------------CT-----------------CACC-CACAACACCTGTAGAC------AC-CGTGTGT
       :            ::                 :.:: :. .. :::: :.::       :: :.::.:
       GGTTTAAGGGGAACTTGAGGGAAGTAGGGAAGACTCCTCTTGGGACCTTTGGAGTAGGTGACACATGAGC
       70        80        90        100       110       120       130

                  80                     90                  100       110
inputs CCAAC------TCTCC-----------CTGAGTA-CTC------CGGGCCA----AGG-AGGGCCATGAT
       :::.:      ::.::            ::::: : :::        :.. :::    ::: .:::: ..:.:
       CCAGCCCCAGCTCACCTGCCAATCCAGCTGAGGAGCTCACCTGCCAATCCAGCTGAGGCTGGGCAGAGGT
      140       150       160       170       180       190       200

                          120       130                140       150       160
inputs TCTTCAG-------------GCTGGAACCCCCGA---GACCAG-C---TTGCTGCGGGTT-TTGTTCCTG
         : ::               ::.::.::: ::..    :.:::: :     ..::::: : .   :: ..::.:
       GGGTGAGAAGAGGGAAAATTGCAGGGACCTCCAGTTGGGCCAGGCCAGAAGCTGCTGTAGCTTTAACCAG
      210       220       230       240       250       260       270

                 170       180       190       200                     210
inputs G-GACTGAGTACCCTTGCTGCCTTCTCCCGAGCTCAGATGGAGTT----GCA---------CGTGCCC--
       . ..:: ::.  :::  :::      :: ::..  .:::.: ..:::        :::               :..: ::
       ACAGCTCAGA--CCTGTCTGGAGGCTGCCAGTGACAGGTTAGGTTTAGGGCAGAGAAGAAGCAAGACCAT
      280       290       300       310       320       330       340

                                   220          230       240       250
inputs ----------------CC---------GGGC-CTCAA--CAAATTGGAAG-CGGTAGAGGGAGAAGAAGTG
                        ::          ::.: :::..  :::.. .::..: : :: :: :    ..    .:::
       GGTGGGGAAGATGTGGCCTGTGTTGTGGACACTCTGTGCAGTCAGGGTGACCGTCGATGCCATCTCTGTG
        350       360       370       380       390       400       410

        260       270              280       290                 300
inputs GTGCTCCCCGCCTG--GTACA-CGA---TGGCACGGGAGGAGT----------CGTGGTCC---------
       :.. .: ::::  :   ::.:. ::.     : ::: ::.:.::::             : :: .::
       GAA-ACTCCGCAGGACGTTCTTCGGGCTTCGCAGGGAAAGAGTGTCACCCTGCCCTGCACCTACCACACT
        420       430       440       450       460       470       480

                    310       320            330                340       350
inputs --CACC-CC---CGGGAGGTGCCCATCCT----GATCTGGTTCT------TGGAACAAGAAGGGAAGGAA
         :::: ::    ::.:::: .:  :: :.     ::: .: : ::             : ..::...:::::.: :
       TCCACCTCCAGTCGAGAGGGACTTATTCAATGGGATAAGCTCCTCCTCACTCATACGGAAAGGGTGGTCA
        490       500       510       520       530       540       550

        360       370                           380       390       400
inputs CCAAACCAGGTGTTGTCTTA------------------CATTAATGGAGTCATGACAAATAAACCTG---
       :...::.  :   ...:..:                      :.::::...::.:::. :.::. ..:.::..
       TCTGGCCGTTTTCAAACAAAAACTACATCCATGGTGAGCTTTATAAGAATCGCGTCAGCATATCCAACAA
        560       570       580       590       600       610       620

              410       420                      430       440       450
inputs ----GAACAGCCCTGGTCCAC--TCT------ATCT------CTTCACGGAATGTGTC-CCTGCG-----
           ::.::: :: .  ::.:  ::.         :::.         :.: .: :: .. : : :::.::
       TGCTGAGCAGTCCGATGCCTCCATCACCATTGATCAGCTGACCATGGCTGACAACGGCACCTACGAGTGT
        630       640       650       660       670       680       690

                    460       470       480          490       500
inputs -C-------CTGGGGGCACTCCAGGAGGGAGACTCTGGGAC---TTACCGCTGTTCTGTCAATGTGC---
        :         :::. : :: .::.::::::: .::.: ..:.:      : .::::     :   :::   :::: 
```

FIG. 26A

```
        TCTGTCTCGCTGATGTCAGACCTGGAGGGCAACACCAAGTCACGTGTCCGCCTGTTGGTCCTCGTGCCAC
           700       710       720       730       740       750       760

                  510       520       530       540       550
inputs  ------AGAATGATGAAGGCAA--AAGTATAGGCCACA----GCATCAAAAGCATA--GAGCT--CAA--
        CCTCCAAACCAGAATGCGGCATCGAGGGAGAGACCATAATTGGGAACAACATCCAGCTGACCTGCCAATC
           770       780       790       800       810       820       830

       560       570       580       590       600       610       620
inputs AGTGCTGGTTCCTCCAGCTCCTCCATCCTGTAGTTTACAGGGTGTAC--CCTATGTCGGGA----CCAAT
       AAAGGAGGGCTCACCAACCCCTCAGTACAGCTGGAAG-AGGTACAACATCCTGAATCAGGAGCAGCCCCT
          840       850       860       870       880       890       900

                   630       640       650                            660
inputs GT---GACC-----CTGAACTGCAAGTCCCCAAGGAGTAAA---CC---------------TACTGC-TC
       GGCCCAGCCAGCCTCAGGTCAGCCTGTCTCCCTGAAGAATATCTCCACAGACACATCGGGTTACTACATC
          910       920       930       940       950       960       970

         670           680           690            700          710
inputs AGTACCA--------GTGGGAGAG--GCTG----GCCCCATC-CT----CC--CAGGTCT---TCTTTGG
       TGTACCTCCAGCAATGAGGAGGGGACGCAGTTCTGCAACATCACGGTGGCCGTCAGATCTCCCTCCATGA
          980       990      1000      1010      1020      1030      1040

               720        730       740           750           760
inputs AC-CAGCCTTAGATG----CTGTTCGTGGATCTTTAAAGC-----TCACTAACCTT----TC--CAT---
       ACGTGGCCCTGTATGTGGGCATCGCGGTGGGCGTGGTTGCAGCCCTCATTATCATTGGCATCATCATCTA
         1050      1060      1070      1080      1090      1100      1110

                                         770       780       790       800
inputs ----------TGCCATG--------------TCTGGAGTCTATGT--CTGCAAGGCTCAAAACAGAGTGG
       CTGCTGCTGCTGCCGAGGGAAGGACGACAACACTGAAGACAAGGAGGATGCAAGGC-CGAACCGG-GAAG
         1120      1130      1140      1150      1160      1170      1180

         810          820         830                  840
inputs GCTTTG-----CCA--AGTGCAAC---GTGACCTT-----------GGACGTGATG-------ACAGG--
       CCTATGAGGAGCCACCAGAGCAGCTAAGAGAACTTTCCAGAGAGAGGGAGGAGGAGGATGACTACAGGCA
         1190      1200      1210      1220      1230      1240      1250

           850       860                                       870       880
inputs ----GTCCAAGGCTGCAGTGGTCG--------------------------CTGG--AGCAGTTGTGGG
       AGAAGAGCAGAGGAGCACTGGGCGTGAATCCCCGGACCACCTCGACCAGTGACAGGCCAGCAGCAGAGGG
         1260      1270      1280      1290      1300      1310      1320

             890       900                 910                        920
inputs CA-CTTTTGTTGGGTTGGTG----------CTGATAGCTGGGCT---------------GGTCCTGTT--
       CGGCGGAGGAAGGGTTAGGGGTTCATTCTCCCGCTTCCTGGCCTCCCTTCTCCTTTCTAAGCCCTGTTCT
         1330      1340      1350      1360      1370      1380      1390

                      930                                           940
inputs -----------GTACCAG---------------------CGCC--------------GGAGCAAGAC---
       CCTGTCCCTCCATCCCAGACATTGATGGGGACATTTCTTCCCCAGTGTCAGCTGTGGGGAACATGGCTGG
         1400      1410      1420      1430      1440      1450      1460

         950                  960             970       980
inputs CTTGGAA-----------GAGCTGG-CCAA-TGA------TATCAAG-GAAGATGCC----------ATT
       CCTGGTAAGGGGGTCCCTGTGCTGATCCTGCTGACCTCACTGTCCTGTGAAGTAACCCCTCCTGGCTGTG
         1470      1480      1490      1500      1510      1520      1530

          990       1000       1010                            1020
```

FIG. 26B

```
inputs GCTCCC----CGGACCTTGCCTT------GGACCAA-----AGGCTC----------------AGACACAA
       .:.::     :::.::: ::: :      .:::::.     :: :::                .:.:: .:
       ACACCTGGTGCGGGCCTGGCCCTCACTCAAGACCAGGCTGCAGCCTCCACTTCCCTCGTAGTTGGCAGGA
         1540      1550      1560      1570      1580      1590      1600

        1030      1040      1050      1060      1070                1080
inputs TCTCCAAGAATGG-GACACTTT-CTTCGGTCACCTCAGCAC-GAGCTCT--------GCG--GCCACCCA
       ::::.:.:::   . ..:.:: . :.: :: :.:  : .:.: ::.::::        :::  :::: ::.
       GCTCCTGGAAGCACAGCGCTGAGCATGGGGCGCTCCCACTCAGAACTCTCCAGGGAGGCGATGCCAGCCT
         1610      1620      1630      1640      1650      1660      1670

                      1090              1100                          1110
inputs AGG---------------CTGCTC--CT------CCAAGACCTGG-----CAC----------ATTTACT
       .::                :::::: ::      :::. ::::::     :::           .::::.:.
       TGGGGGGTGGGGGCTGTCCTGCTCACCTGTGTGCCCAGCACCTGGAGGGGCACCAGGTGGAGGGTTTGCA
         1680      1690      1700      1710      1720      1730      1740

        1120                                    1130      1140        1150
inputs C-CCACAC--C---C-----------------AGTGT-----CTCTAGCCAGGCCCTGTCCT---CAC
       : ::::::  :   :                 ::::.     ::  .:::  ::  :: :::    :.:
       CTCCACACATCTTTCTTGAATGAATGAAAGAATAAGTGAGTATGCTTGGGCCCTGCATTGGCCTGGCCTC
         1750      1760      1770      1780      1790      1800      1810

              1160      1170      1180      1190       1200      1210
inputs CAAGACT---GCCCAGGGTAGATGAACC-CCCACCTCAGGCAGT--GTCCCTGACCC--CAGGTGGGGTT
       ::. .:     :::.     :.     ::  :::.   :.: ::::  :: ::..::::  :.:: ..::
       CAGCTCCCACTCCCTTTCCAACCTCACTTCCCGTAGCTGCCAGTATGTTCCAAACCCTCCTGGGAAGGCC
         1820      1830      1840      1850      1860      1870      1880

               1220      1230                              1240      1250
.nputs TCTTC-------TTCTGCTCTGAGCC------GCATGGG--------------TGCTGTGCCTGT-GATG
       .: ::       : ::::.:.:. ::      ::.:  :               . :: ::::::: .::.
       ACCTCCCACTCCTGCTGCACAGGCCCTGGGGAGCTTTGCCCACACACTTTCCATCTCTGCCTGTCAATA
         1890      1900      1910      1920      1930      1940      1950

          1260      1270      1280      1290         1300      1310
.nputs --GTGCCTG---CACAGAGTCAGGCT-GGGTCTCTTGTGTGA---TAGCCCAGGCACTCATTAGCTACAT
         ::.::::   :.: ..: : . :: ...::.:..: .: .   ::.:::.. : :: :::. : ::::
       TCGTACCTGTCCCTCCAGGCCCATCTCAAATCACAAGGATTTCTCTAACCCTATC-CTAATTGTCCACAT
         1960      1970      1980      1990      2000      2010      2020

         1320      1330      1340        1350      1360      1370
nputs -C-TGGTATCTGACCT--TTCTGTAAAGGTC-TCCTT--GTGGCACAGAGGACTCAATCTT--GGGAGGA
       : :::.:.:...::  :.:: :..    .: :::..   .::: :: :.:.:.::.::::  :.: :..
       ACGTGGAAACAATCCTGTTACTCTGTCCCACGTCCAATCATGGGCCACAAGGCACAGTCTTCTGAGCGAG
         2030      2040      2050      2060      2070      2080      2090

      1380      1390      1400        1410                1420
nputs TGCCCACA---TTCTAGACCTCCAG-TCCTTTG--CT---CCTA--CCTC----CTT---CTAT---TGT
       ::: :.::   :. :::: : :::: ::::: :  :.    :::.   ::::    :::   ::.:    ::.
       TGCTCTCACTGTATTAGAGCGCCAGCTCCTTGGGGCAGGGCCTGGGCCTCATGGCTTTTGCTTTCCCTGA
         2100      2110      2120      2130      2140      2150      2160

         1430      1440      1450
nputs TG----GAATACTGG-GCC--TC--AGTAAG-ACTAAA-------------ATCTG--------------
       .:     .....:::: :::  ::  :::..: :::.::              :.:::
       AGCCCTAGTAGCTGGCGCCCATCCTAGTGGGCACTTAAGCTTAATTGGGGAAACTGCTTTGATTGGTTGT
         2170      2180      2190      2200      2210      2220      2230

               1460                 1470      1480
nputs --------------GGTCA-------------AAGGACAAAAGGAGGAAAT------GGACC--------
                     ::::.             ...:::: :.::: ::..        ..:::
       GCCTTCCCTTCTCTGGTCTCCTTGAGATGATCGTAGACACAGGGATGATTCCCACCCAAACCCACGTATT
         2240      2250      2260      2270      2280      2290      2300

         1490      1500      1510       1520             1530
nputs -------TGAGGTAGG---GGGTTGGGAGTGAGGAGGCT-TCACTT-----CCTCCCTGCT-----TCT-
              :::: ::..   :..:::. . ..:: ...:. .:::..       : : : :::.       :::
       CATTCAGTGAGTTAAACACGAATTGATTTAAAGTGAACACACACAAGGGAGCTTGCTTGCAGATGGTCTG
         2310      2320      2330      2340      2350      2360      2370
```

FIG. 26C

```
          1540      1550                1560      1570                1580
inputs ---CCCTGAAGCCAGATGAATGCT------GC--GGAAGATCGGCT----------ACCCTCCAAGGGCT
          : ::.. ::.:.:.:.: ::       ::  :.:..:: :::.          ::::.: ..::: :
       AGTTCTTGTGTCCTGGTAATTCCTCTCCAGGCCAGAATAATTGGCATGTCTCCTCAACCCACATGGGGTT
          2380      2390      2400      2410      2420      2430      2440

         1590      1600      1610      1620        1630      1640
inputs C-TGGAGGAGACTGCCAGTCAGTGATGC--CCCTGGCTCTG---TGATCTGTACAACACCC-TTATCTAA
       : :::. :.  :::: .  :..:.   :  ::::::: :::   .:  :. :. ..:.:  ::.::::..
       CCTGGTTGTTCCTGCATCCCGATACCTCAGCCCTGGCCCTGCCCAGCCCATTGGGCTCTGGTTTTCTGG
          2450      2460      2470      2480      2490      2500      2510

     1650      1660      1670      1680                1690
inputs TG---CTGTCCTT-TGCCGTTCGCTCCATCTCC--CTGT---------ATTAATATAAC-----------
       ::   ::::::: .:::  :: :.: . ::::  ::::          :::. :. .::
       TGGGGCTGTCCTGCTGCC-CTCCCACAGCCTCCTTCTGTTTGTCGAGCATTTCTTCTACTCTTGAGAGCT
          2520      2530      2540      2550      2560      2570      2580

                   1700                1710                              1720
inputs CTGTC----------CTGCT---GGCT----------TGGCTGG---------------GTTT--TGTTG
       :.: :          :::::  .: ::          :::::::                ::::  :.:::
       CAGGCAGCGTTAGGGCTGCTTAGGTCTCATGGACCAGTGGCTGGTCTCACCCAACTGCAGTTTACTATTG
          2590      2600      2610      2620      2630      2640      2650

               1730      1740        1750              1760      1770
inputs ------TAGCAGGGGGATAGGAAAGACATTT--TAAAATCTG------ACTTGAAATTGATGTTTTTGTT
             :. :.::. ::: .:::::.: :.::  ..::::::.      ::::: .::: .: ......:
       CTATCTTTTCTGGATGATCAGAAAAATAATTCCATAAATCTATTGTCTACTTGCGATTTTTTAAAAAATG
          2660      2670      2680      2690      2700      2710      2720

    1780      1790      1800           1810        1820      1830      1840
inputs TTTATTTTGCAAATTTCAATAAAGA----TACATCG---CATTTGCATGGAAAAAAAAAAAAAAAGGGCG
       :.::::::  .:..:. ..:.::..     :.:.::.   ::..:::.:  :..::.::.::::..: : :
       TATATTTTTATATATATTGTTAAATCCTTTGCTTCATTCCAAATGCTTTCAGTAATAATAAAATTGTGGG
          2730      2740      2750      2760      2770      2780      2790

inputs GCCGC
          :
       T--GG
```

FIG. 26D

```
ALIGN calculates a global alignment of two sequences
 version 2.0uPlease cite: Myers and Miller, CABIOS (1989)
> hT258 n.a.                                         1869 aa vs.
> pecam n.a.                                         2557 aa
scoring matrix: pam120.mat, gap penalties: -12/-4
40.5% identity;        Global alignment score: 1546

                                             10         20
inputs G---TC----------GACC------------------CAC---GCGTNCNTC-CAGCGTN---------
       :   ::          ::::                  :::   ::: . .:: ::.:: .
       GAATTCCGGGAGAAGTGACCAGAGCAATTTCTGCTTTTCACAGGGCGGGTTTCTCAACGGTGACTTGTGG
               10        20        30        40        50        60        70

          30        40         50        60         70         80
inputs -CGGAGCCGCC--CTGGG--TGTCAGCGGCTCGGCTCCCGCGCACGCT---CCGGC---CGTCGC-----
        :.:.:::  :  :::.:  .::::  ::: ::.    : : .:. .::    :: ::   : ::.:
       GCAGTGCCTTCTGCTGAGCGAGTCAT-GGCCCGAAGGCAGAACTAACTGTGCCTGCAGTCTTCACTCTCA
               80        90        100       110       120       130

                  90         100        110          120       130
inputs ----GCAGCCTCGGCA--CCTGCAGGTCCG---TGCGTCCCG-----CGGCTGGCGCCCCTGACTCCGTC
           ::::::  :: .  :: . .:: ::.   :: : :  :     : :::.:.: :  ::: ::: ::
       GGATGCAGCCGAGGTGGGCCCAAGGGGCCACGATGTGGCTTGGAGTCCTGCTGACCCTTCTG-CTCTGTT
      140       150       160       170       180       190       200

        140      150       160         170            180
inputs CCGGCCAGGGAGGGCCATGATTTCCCT--CCCGG--GGCC-------CCTGGTGA-CCAAC--------T
       : .:::. : :::: ::.::...: ::  : :..  ..:       : ::..:: ::..:         .
       CAAGCCTTG-AGGGTCAAGAAAACTCTTTCACAATCAACAGTGTTGACATGAAGAGCCTGCCGGACTGGA
         210       220       230       240       250       260       270

        190         200       210                220        230
inputs TGNTGCGGTTT---TTGTTCCTGGGGCTG-AGTGC--C-C-----TC-GCGCCCCC-CTCGCG---GGCC
        :.:::....:   ..:..::::.  ::: :::::  : :     :: ::.:: :: :::.::    .:::
       CGGTGCAAAATGGGAAGAACCTGACCCTGCAGTGCTTCGCGGATGTCAGCACCACCTCTCACGTCAAGCC
        280       290       300       310       320       330       340

      240       250                                  260       270       280
inputs -CAGCTGCAACTGC---------------ACTTGC-------C-----CGCCAACCGGTTGCAGGCGGTG
        ::::. ::. :::               :: :::       :     : ::. :  :..: . .:.:.:
       TCAGCACCAGATGCTGTTCTATAAGGATGACGTGCTGTTTTACAACATCTCCTCCATGAAGAGCACAGAG
        350       360       370       380       390       400       410

           290              300       310           320       330      340
inputs GAGGAGGGGGA-----AAGT--GGTGCTTCAGCA-TGGTACACCT---TGCACAGGGAGGTGTCTTCATC
       ..  :    ..      ::::  ::. ::. ..:. .:: :::  :    :: ::.: ::  ::: ..::.:
       AGTTATTTTATTCCTGAAGTCCGGATCTATGACTCAGGGACATATAAATGTACTGTGAT-TGTGAACAAC
        420       430       440       450       460       470       480

                   350        360        370        380       390
inputs CCAG------CCA-TGGGAGGTGCC--CTTT--GTGATGTGGTTCTTCAAACAGAAAGAAAAGGAGGATC
         ::       ::: :: ...::.::  :: :  :::... :. :    ::..:  :..:..: . .:::
```

FIG. 27A

```
         AAAGAGAAAACCACTGCAGAGTACCAGCTGTTGGTGGAAGGAGTGCCCAGTCCCAGGGTGACACTGGACA
          490       500       510       520       530       540       550

        400       410       420            430        440            450
inputs AGGTGTTGTCCTACATCAATGGGGTCA--------CAACAAG-CAAACCTGGAGTAT------CCTTGG-T
       ::...  .: ::..: . ..:::::.::.       :::::..  :...:: .::: :.      ::.. . .
       AGAAAGAGGCCATCCAAGGTGGGATCGTGAGGGTCAACTGTTCTGTCCCAGAGGAAAAGGCCCCAATACA
        560       570       580       590       600       610       620

         460                  470         480         490              500
inputs CTACTC----------CATGCCCTCCCGGAACC--TGTCCCTGC-GGGTGGAGGG------TCTC-----
       ::.:.:          :.::  ::    :::    ::  :  .:: :.....:::.:      ::::
       CTTCACAATTGAAAAACTTGAACTAAATGAAAAAATGGTCAAGCTGAAAAGAGAGAAGAATTCTCGAGAC
        630       640       650       660       670       680       690

          510              520            530       540             550
inputs CAGGAGAAAG--ACTCTGG----CCCCTAC----AGCTGCTCCGTGAATGTGC------AAGACAAACAA
       :::.: ...:  : .::::     :::: .     :.:.: .::: :..: . :       :.:.:::.:.:
       CAGAATTTTGTGATACTGGAATTCCCCGTTGAGGAACAGGACCGCGTTTATCCTTCCGATGTCAAGCTA
        700       710       720       730       740       750       760

          560       570            580                  590
inputs GG--CAAATCTAGGGGCCA----CAG-CATCAAAA----CCTTA---------GAACTCAATG--------
       ::  ::..:::.::. :::     ::: : :::.::    ::...         :..:.: .::
       GGATCATTTCTGGGATCCATATGCAGACCTCAGAATCTACCAAGAGTGAACTGGTCACCGTGACGGAATC
        770       780       790       800       810       820       830

        600                610            620                630
inputs -TACT---------GGTTCCTC--CAGCTCCTCC------ATCCTG--------C-CGTCTCCA--GGGTG
       :.::          .::::::.:  :::: ::.::       ::: ::         : :. :::::    ..:
       CTTCTCTACACCCAAGTTCCACATCAGCCCCACCGGAATGATCATGGAAGGAGCTCAGCTCCACATTAAG
        840       850       860       870       880       890       900

      640        650       660       670              680              690
inputs TGCCCCATG-TGGGGGCAAACGTGACCCTG-AGCTGCCAG---TC------TC--------CAAGGAGTAAG
       ::: ::::  ..: :.:. :: ::.:::.: :: : ::::    ::      ::         ::::: :...:
       TGCACCATTCAAGTGACTCACCTGGCCCAGGAGTTTCCAGAAATCATAATTCAGAAGGACAAGGCGATTG
        910       920       930       940       950       960       970

                                        700             710            720
inputs ---CCC--------------------GCTGT---C-----CAATACCAGTG-GGATC------GGCAGCTT
         :::                     :::::   :     ::. .::: : ::: :        ::::.::.
       TGGCCCACAACAGACATGGCAACAAGGCTGTGTACTCAGTCATGGCCATGGTGGAGCACAGTGGCAACTA
        980       990      1000      1010      1020      1030      1040

        730               740        750        760        770
inputs C-CATCCT---------TCCAGAC---TTTCTTTG--CACCAGCATTAGATGTCATCCGTG--GGTCTTTA
       : :.: :.         ::::: :   :.:: ..:  :: :::::: :. ::::.:  ..   :..::.:.
       CACGTGCAAAGTGGAGTCCAGCCGCATATCCAAGGTCAGCAGCATC-GTGGTCAACATAACAGAACTATT
       1050      1060      1070      1080      1090      1100      1110

     780       790       800          810            820          830
```

FIG. 27B

```
inputs AGCCTCACC-AACCTTTCGTCTTCCAT-----GGCTGGA-----GTCTATGTCTG--CAAGGCC--CACA
       . ::. .:: .: ::   .::::::.:     . :::::     :: .:.:.::: : .: ::  :.:
       TTCCAAGCCCGAACTGGAATCTTCCTTCACACATCTGGACCAAGGTGAAAGACTGAACCTGTCCTGCTCC
        1120      1130      1140      1150      1160      1170      1180

          840                 850                     860       870
inputs ATG--AGGTG-------GGC--ACTGC-CCA-----ATGTAA--------TGTGACGCTGG---AAGTGA
       ::   ::::.:       .::  ::: : :::      :.: ::        ::::.:.:.:.  :::. .
       ATCCCAGGAGCACCTCCAGCCAACTTCACCATCCAGAAGGAAGATACGATTGTGTCACAGACTCAAGATT
        1190      1200      1210      1220      1230      1240      1250

       880            890          900       910         920         930
inputs GCAC----AGGGCCT-GGAG-CTG-CAGTGGTTGCTGAAGCTGT--TGTGGGTACC--CTGGTTGGACTG
       :::     : .:::: ..:: : : :::::: .   :..: :::   :: .::::    :... :::.:..
       TCACCAAGATAGCCTCAAAGTCGGACAGTGGGACGTATATCTGCACTGCAGGTATTGACAAAGTGGTCAA
        1260      1270      1280      1290      1300      1310      1320

         940       950       960                   970        980
inputs GGGTTGCTG-GCTGGGCTGGTCCTCTTGTA-------C-CACC--GCCGGGG----CAAG----GCCCTG
       :....::.. .:.:   :.:.:  :: :.:.       : :.::  ::: .::     :...     ::::.:
       GAAAAGCAACACAGTCCAGATAGTCGTATGTGAAATGCTCTCCCAGCCCAGGATTTCTTATGATGCCCAG
        1330      1340      1350      1360      1370      1380      1390

        990      1000      1010         1020      1030                 1040
inputs GAGGAGCCAGCCAATGATATCAAG--GAGGATG-CCATTGCTCCCCGGACC------CT--GCC-----C
       . :::   . : .:..: ..::..  .. ::.: ::.::::     ::..:      ::  :::     :
       TTTGAG--GTCATAAAAGGACAGACCATCGAAGTCCGTTGCGAATCGATCAGTGGAACTTTGCCTATTTC
        1400      1410      1420      1430      1440      1450      1460

                 1050      1060      1070      1080      1090
inputs TGGCC--CAA--GAGCTCAGACACAATCTCCAAGAATGGGACCCTTTCCTCTGTCA--CCTCCG-----C
       : .::  :..   .:. .::.. : :.: :   .:::::.: ::: . . :::... .  ::: ::     :
       TTACCAACTTTAAAAACAAGTAAAGTTTTGGAGAATAGTACCAAGAACTCAAATGATCCTGCGGTATTC
        1470      1480      1490      1500      1510      1520      1530

     1100          1110              1120                     1130
inputs A----CGAGCCCTCCG--GCCACC------CCA-----TGGC---------CC--TCCCAGGCCT------
       :    :.: :::.: :  : :. :       :::      : ::          ::  ::::: :::.
       AAAGACAACCCCACTGAAGACGTCGAATACCAGTGTGTTGCAGATAATTGCCATTCCCATGCCAAAATGT
        1540      1550      1560      1570      1580      1590      1600

          1140                 1150                1160      1170
inputs -------GGTGCATTG------------ACCCCC---------ACGCCCAG---TCTATCCAGCCAGG---
              ::: :. .:            : ::::          : : ::::   :::::::.: ::.:
       TAAGTGAGGTTCTGAGGGTGAAGGTGATAGCCCCGGTGGATGAGGTCCAGATTTCTATCCTGTCAAGTAA
        1610      1620      1630      1640      1650      1660      1670

                                                               1180
inputs -----------C---------C-------CTGC--------------------------CC--TCACCAAG
                  :         :       ::::                          ::  :::::.:
       GGTGGTGGAGTCTGGAGAGGACATTGTGCTGCAATGTGCTGTGAATGAAGGATCTGGTCCCATCACCTAT
        1680      1690      1700      1710      1720      1730      1740
```

FIG. 27C

```
          1190      1200      1210      1220      1230      1240
inputs ACATGC--CCACGACAGATGGGGCCCACCCT-CAACCAA-TATCCCC-----CATCCCTGG---TGGGGT
       : .:    : . :: :.: .:::: ::::: :.: ::: :..:: :      : .:::.::   :  ::.
       AAGTTTTACAGAGAAAAAGAGGGCAAACCCTTCTATCAAATGACCTCAAATGCCACCCAGGCATTTTGGA
          1750      1760      1770      1780      1790      1800      1810

          1250      1260      1270               1280      1290      1300
inputs TTTTTCCTTTGGCTT---TGAGCCGCATGGGTG-------CTG---NGCCTGTGATGGNGCCTGCC----
       .. :   ..::::.   .:.. :. ..:::.:        :::   .:::: .: .:.:::..::
       CCAAGCAGAAGGCTAGCAAGGAACAGGAGGGAGAGTATTACTGCACAGCCTTCAACAGAGCCAACCACGC
          1820      1830      1840      1850      1860      1870      1880

                            1310      1320      1330      1340      1350
inputs ---CAGAGTC------------AAGCTGGCTCTCTG-GT-ATGATGACCCCACCACTCATTGG-CTAAAG
          :::.:::             :..:::.:. ::.: :: ::  : .:::::  . . :..:: ::.:.
       CTCCAGTGTCCCCAGAAGCAAAATACTGACAGTCAGAGTCATTCTTGCCCCATGGAAGAAAGGACTTATT
          1890      1900      1910      1920      1930      1940      1950

          1360                1370      1380           1390
inputs GATTTGGG-GTC-TC--------TCCTTCCTATAAGGGTCA------CCTCTAGCA-----CAGAGG----
       : . :::  .:: ::        :: :: :: : . :.:::       ::. ..: .     :.::::
       GCAGTGGTTATCATCGGAGTGATCATTGCTCTCTTGATCATTGCGGCCAAATGTTATTTCTGAGGAAAG
          1960      1970      1980      1990      2000      2010      2020

     1400      1410      1420      1430          1440      1450
inputs CCTGAGTCATG-GGAA---AGAGTCACACTCCTGACCCTTAGTAC----TCTG--CCCCCACCTC-----
       ::...: ::.: .::.    ::.:  : . :::.:.::     :::::    ::::  : :: :: .:
       CCAAGGCCAAGCAGATGCCAGTGGAAATGTCCAGGCCAGCAGTACCACTTCTGAACTCCAACAACGAGAA
          2030      2040      2050      2060      2070      2080      2090

              1460      1470      1480      1490      1500      1510
inputs ----TCTTTAC--TGTGGGAAAACCATC--TCAGTAAGACCTAAGTGTCCAGGAGACAGAAGGAGAA-GA
           ::. ..:  ..:. :.::.: :.:  ::: :: :. :. :.::.:  :..:.:::::.  ... .:
       AATGTCAGATCCCAATATGGAAGCTAACAGTCATTACGGTCACAATGAC--GATGTCAGAAACCATGCAA
          2100      2110      2120      2130      2140      2150      2160

          1520      1530      1540      1550        1560        1570
inputs GGAAGTGGATCTGGAATTGGGAGGAGCCTCCACCCACC-CCTGAC--TCCTCC----TTATGAAGCCAGC
       :::.  .:: .. .::.. .:.:::::::: .   :.:   :  .:  :. :.:      :: ....: :  :
       TGAAACCAATAAATGATAATAAAGAGCCTCTGAACTCAGACGTGCAGTACACGGAAGTTCAAGTGTCCTC
          2170      2180      2190      2200      2210      2220      2230

    1580      1590      1600      1610      1620      1630        1640
inputs TGCTGAAATTAGCTACTCACCAAGAGTGAGGGGCAGAGACTTCCAGTCACTGAGTCTCCCAG---GCC--
       .::::::.. : .:.:    .: :.::..::.::.:: :::  .: .   ::.:.:.   ::.:   ::
       AGCTGAGTCTCACAAAGATCTAGGAAAGAAGGACACAGA-GACAGTGTACAGTGAAGTCCGGAAAGCTGT
          2240      2250      2260      2270      2280      2290      2300

          1650      1660                1670      1680        1690      1700
inputs CCCTTGATCTGTACCCCAC------CCCTA--TCTAACACCACCCTTG--GCTCCCACTCCAGCTC--CCT
       :::: .. : ::.     .:      : :::   .: .: . :.::::::  : . : .    ::::.  ::.
       CCCTGATGCCGTGGAAAGCAGATACTCTAGAACGGAAGGCTCCCTTGATGGAACTTAGACAGCAAGGCCA
```

FIG. 27D

```
             2310      2320      2330      2340      2350      2360      2370

            1710      1720       1730       1740          1750      1760
inputs GTATTGATATAACCTGTCAGG-CTGGCTTGGTTAG-GTTTTACTGGGG----CAGAGGATAGGGA-----
       :.  :: . .. ::::  ::: :.  :.:: :  : :.. .::.:. .    :.:.. .: ..::
       GA--TGCACATCCCTGGAAGGACATCCATGTTCCGAGAAGAACAGATAATCCCTGTATTTCAAGACCTCT
               2380      2390      2400      2410      2420      2430

              1770          1780      1790      1800        1810      1820
inputs -ATCTCTTATTAAAA---CTAACATGAAATATGTGTTGTTTTCATTT--GCAAATTTAAATAAAGATACA
        . :.::::::.:..   ::. : :: .    . .:.. . . ::.::   ::.. :.:. :.  :.:.:.
       GTGCACTTATTTATGAACCTGCCCTGCTCCCACAGAACACAGCAATTCCTCAGGCTAAGCTGCCGGTTCT
     2440      2450      2460      2470      2480      2490      2500

            1830      1840      1850      1860
inputs TAAT---GTTTGTATGAGATAAGAAAAAAAAAAAAAAAGGGCGGCCGC-
       :::.    .:       :.::.::: .......:.:::.:.. .:.:  :
       TAAATCCATCCTGCTAAGTTAATGTTGGGTAGAAAGAGATACAGAGGGG
     2510      2520      2530      2540      2550
```

FIG. 27E

TANGO 281

Input file AthPb81d10.seq; Output File AthPb81d10.pat
Sequence length 1812

```
                                                                  M   R   L        3
GTCGACCCACGCGTCCGGCGGAGGTTGTGGCTGCACCGTGGTCCTGGGCTTGGTCCTGGGCTTG ATG CGT CTG       73

 F   V   R   P   S   V   R   P   A   M   A   A   P   A   P   S   P   W   T   L    23
TTT GTC CGT CCG TCC GTC CGT CCC GCC ATG GCT GCG CCG GCG CCC TCT CCG TGG ACC CTT   133

 S   L   L   L   L   L   L   L   P   S   P   G   A   H   G   E   L   C   R   P    43
TCG CTG CTG CTG TTG TTG CTA CTG CCG TCT CCG GGT GCC CAT GGC GAG CTG TGC AGG CCC   193

 F   G   E   D   N   S   I   P   E   S   C   P   D   F   C   C   G   S   C   S    63
TTC GGT GAA GAC AAT TCG ATC CCA GAG TCC TGT CCT GAC TTC TGT TGT GGC TCC TGT TCC   253

 S   Q   Y   C   C   S   D   V   L   K   K   I   Q   W   N   E   E   M   C   P    83
AGC CAA TAC TGC TGC TCT GAC GTG CTG AAG AAA ATC CAG TGG AAT GAG GAA ATG TGC CCT   313

 E   P   E   S   S   R   F   S   A   H   P   E   T   P   E   Q   L   G   S   A   103
GAG CCA GAG TCC AGC AGA TTT TCC GCC CAC CCG GAG ACA CCA GAA CAG CTG GGT TCA GCG   373

 L   K   Y   Q   S   S   L   D   S   D   N   M   P   G   F   G   A   T   V   A   123
CTG AAG TAT CAG TCC AGT CTT GAC AGT GAC AAC ATG CCA GGG TTC GGA GCG ACC GTG GCC   433

 I   G   L   T   V   F   V   V   F   I   A   T   I   I   V   C   F   T   C   S   143
ATC GGC CTG ACC GTC TTC GTG GTG TTT ATC GCT ACC ATC ATT GTG TGC TTT ACC TGC TCC   493

 C   C   C   L   Y   K   M   C   C   R   P   R   P   V   V   S   N   T   T   T   163
TGC TGC TGT CTA TAT AAG ATG TGC TGC CGC CCA CGA CCT GTC GTG TCC AAC ACC ACA ACT   553

 T   T   V   V   H   T   A   Y   P   Q   P   Q   P   V   A   P   S   Y   P   G   183
ACT ACC GTG GTT CAC ACC GCT TAC CCT CAG CCT CAA CCT GTG GCC CCC AGC TAT CCT GGA   613

 P   T   Y   Q   G   Y   H   P   M   P   P   Q   P   G   M   P   A   A   P   Y   203
CCA ACA TAC CAG GGC TAC CAT CCC ATG CCC CCC CAG CCA GGA ATG CCA GCA GCA CCC TAC   673

 P   T   Q   Y   P   P   P   Y   L   A   Q   P   T   G   P   P   A   Y   H   E   223
CCA ACG CAG TAC CCT CCA CCC TAC CTG GCC CAG CCC ACA GGG CCA CCA GCC TAT CAT GAG   733

 T   L   A   G   A   S   Q   P   P   Y   N   P   A   Y   M   D   P   P   K   A   243
ACG TTG GCT GGA GCC AGC CAG CCT CCA TAC AAC CCG GCC TAC ATG GAT CCC CCA AAG GCA   793

 V   P   *   246
GTT CCC TGA  802

GCCTGCCCCCAGCCTCTTTGGCTAACATTTGATTATGTCATGTGTGTGAGTGCTATGCAGAGTTCTTTACTGCTGTC   881

TGTGGTGCGTGTGCCTTGTCTAGACATGTGGCTTCCTCTGCTGATGACCAGGTAGGCACAAATCTTACCAGTGCTGGTT   960

GGGACCAATCTGTTTTCTTCCTCACTTGAAATTGTAATTTCTGAAATTTCAAGTAAATTAAAAACAATAGGGTAGGAGG 1039

TATTTCCCGCTTCACCCCAAGGTGACCAGCCATAGCCTGCCACACATAGGAGAGCAAGCTTTTTGTGGGTCCATGTCCT 1118

GCTTTGGGGAGTAGCCAGCTAGCTGCTGCTATGGGTTTATTCCCAGGGCTTGGCTGCATTTAGCTGGACAGAGAACAAG 1197

GGGCCTCAGTGGCAGTGGGTCAGTGACTGATGTCAGAGCACACTAGGCAGAGAGCCCCGTCCGTCTCCATCAGCTGTCT 1276

GTCTGGACGGTCCCACTGTCTTTCCTGGGACTATGTAGAGGGCCACATGTATTCACTATTCAGGCTCCAGTGGCTTCCA 1355

GGCCAGGGGCCTCTGTCTACTACACACTCTGGTTTCTCCCTACAGTGTCTTTTTACGATTAGCCAAACATATTGCCTGT 1434

TTTTTGTATCCAGATGTGTGATAATTGGTGAGGTTGAAATCCTTGGTTCCTGGAGAACAGGAAACCTGACCTCTGACAG 1513
```

FIG. 28A

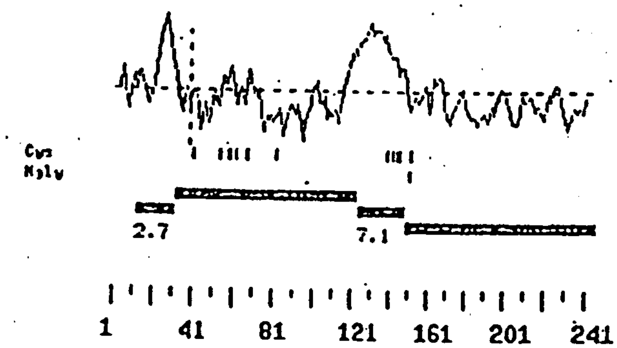
TCCGTTTCCCTTGACACCAGCTTCATAGAATACCTGACTCCTGTACTACAGTCCAGTTTGTTCCAGTAGCAGGGACACC 1592

AGGGCCAGGGGTTATCTGGACCAAGGGTGGGGGTGGAGAGCCTGGATGGTAGCTCTGGACCAGATGTGAATGCCTCCAT 1671

ATTCCCTGTTGGTTCCTGTTTCACTGGCTGTTTTAGTTTTGTGTTAATTGGTGTTTCTGAGCATTCAAACTCCGCACCC 1750

TCGTTTATAATAAATGAATATTTGGAAAAAAAAAAAAAAAAAAAAAAAAA 1812

FIG. 28B



>hT281
MRLFVRPSVRPAMAAPAPSPWTLSLLLLLLLPSPGAHGELCRPFGEDNSIPESCPDFCCG
SCSSQYCCSDVLKKIQWNEEMCPEPESSRFSAHPETPEQLGSALKYQSSLDSDNMPGFGA
TVAIGLTVFVVFIATIIVCFTCSCCCLYKMCCRPRPVVSNTTTTTVVHTAYPQPQPVAPS
YPGPTYQGYHPMPPQPGMPAAPYPTQYPPPYLAQPTGPPAYHETLAGASQPPYNPAYMDP
PKAVP

FIG. 29

```
Alignments of top-scoring domains:
PSBH: domain 1 of 1, from 97 to 146: score 5.5, E = 8.5
                   *->ktalgelLkPlnseyGKvaPgWGttplmgvfmalfavFLliileiYn
                      +lg+ Lk   s     +Pg+G t+ +g  +++f+vF+  i+  +
      hT281    97     PEQLGSALKYQSSLDSDNMPGFGATVAIG--LTVFVVFIATIIVCFT 141

                   ssvll<-*
                   s
      hT281   142 CSCCC    146
```

FIG. 30

Input file T281Atmea49d3; Output File T281Atmea49d3.pat
Sequence length 1858

```
GTCGACCCACGCGTCCGCGCGGAGGTTGCGGCGGCACCGTGGTCTTGGGCTTGGTCCGTCTGTTCGTCCGTCCGTTGGT   79

            M   A   A   P   A   P   S   L   W   T   L   L   L   L   L   L    17
CTGTCCCGCC ATG GCT GCG CCG GCG CCC TCT CTG TGG ACC CTA TTG CTG CTG CTG TTG CTG   140

L   P   P   P   P   G   A   H   G   E   L   C   R   P   F   G   E   D   N   S    37
CTG CCG CCG CCT CCG GGT GCC CAT GGT GAG CTG TGC AGG CCC TTT GGT GAA GAC AAT TCG  200

I   P   V   F   C   P   D   F   C   C   G   S   C   S   N   Q   Y   C   C   S    57
ATC CCA GTG TTC TGT CCT GAT TTC TGT TGT GGT TCC TGT TCC AAC CAA TAC TGC TGC TCG  260

D   V   L   R   K   I   Q   W   N   E   E   M   C   P   E   P   E   S   S   R    77
GAC GTG CTG AGG AAA ATC CAG TGG AAT GAG GAA ATG TGT CCT GAG CCA GAG TCC AGC AGA  320

F   S   T   P   A   E   E   T   P   E   H   L   G   S   A   L   K   F   R   S    97
TT TCC ACC CCC GCG GAG GAG ACA CCC GAA CAT CTG GGT TCA GCG CTG AAA TTT CGA TCC  380

S   F   D   S   D   P   M   S   G   F   G   A   T   V   A   I   G   V   T   I   117
GT TTT GAC AGT GAC CCT ATG TCA GGG TTC GGA GCG ACC GTC GCC ATT GGC GTG ACC ATC  440

F   V   V   F   I   A   T   I   I   I   C   F   T   C   S   C   C   C   L   Y   137
TT GTG GTG TTT ATT GCC ACT ATC ATC ATC TGC TTC ACC TGC TCC TGC TGC TGT CTG TAT  500

K   M   C   C   P   Q   R   P   V   V   T   N   T   T   T   T   T   V   V   H   157
AG ATG TGC TGC CCC CAA CGC CCT GTC GTG ACC AAC ACC ACA ACT ACT ACC GTG GTT CAT  560

A   P   Y   P   Q   P   Q   P   Q   P   V   A   P   S   Y   P   G   P   T   Y   177
CC CCT TAC CCT CAG CCT CAA CCT CAA CCT GTG GCC CCC AGC TAT CCT GGA CCA ACA TAC  620

?   G   Y   H   P   M   P   P   P   A   R   N   A   S   S   T   L   P   N   A   197
G GGC TAC CAT CCC ATG CCC CCC CCA GCC AGG AAT GCC AGC AGC ACC CTA CCC AAC GCA  680

    P   T   T   L   P   G   P   A   H   R   A   A   T   L   P   *               214
A CCC ACC ACC CTA CCT GGC CCA GCC CAC AGG GCC GCC ACC CTA CCA TGA               731

CCTTGGCTGGAGCCAGCCAGCCTCCATACAACCCGACCTACATGGATTCCCTAAAGACAATTCCCTGAACCTGCCCC  810

GCCTCTTTGGCTGCCATTTATGTCGTGTGTGAGTGAGTGATACGCAGAGTTCTTTACTGCTGTCTGTGGTGTGTGTG  889

TTGTCTAGACATGTGGCTTCCTCTGCTGTTGACCAGGTAGGCGCAAGTCTTACCAGTGTGGGTCGGGACCAACCTGT  968

TCTTCCTCACTTGAAATTGTACTTTCTGAAATTTCAAGCAAATTAAAAACAATAAGGTAGGAGGTATTTCCCACGTC  1047

CCCAAGGTGACCAGCCATGGCCTGTCATACTTAGGAGAGCAAGCTTTTTGCGGGTACAGAGCAGGCTTTGGGGGGTA  1126

CAGCTAGCTGCTGCTAGGCCTTTATTCCCAGGGTTTGGCTGCATTGGCAGTGAGGCAGGTGGCTGGGGGTGACACCA  1205

TGACAAGGGGACTCAGTGGCAGGGGGTCACACCAGGCAGAACACCATACACTCTCCATCAGCTGTCTGTCTGGATGT  1284
```

FIG. 31A

ACTGTCCTTCCCGGGGCTGTATAGAGGGCCACATGTGTTCACTATTCAGGCTCCACTGGGGGAATTTTCCTACCTTTG 1363

TGGCTTGGCTCCTGCTCCCAGGCCAGGGACCTCGGTCTGTCTACTACACACTCTGGTTTCTCCCTGCACTGTCTTTTT 1442

CTGTTAGCCAAACATTTTGCCTGTTTTCTGTCTCCAGATGTGTGATAATTGGTGTGAGGTTGAAATCCCTGGTTCCTG 1521

AGGACAGACAACCTGACCTCCGACTGTCAGTTTCCCTTGACACCATCTTCATAGAAATACCTGACTCCTGTACCACAG 1600

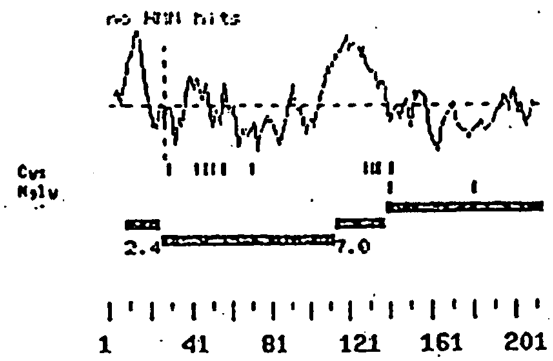
CCAGTTTGTCCCAGTAGCAGGGACACCAAGGCCAATGGGTTATCTGGACCAAAGGTGGGGTGGAGGGCCTAGATGGTA 1679

CTCCGGCCCAGATGTGAATACCTCCATATTCCCTGTTGGTTCCTGTTTCACTGGCTGTTTTAGCTTTGTGTTGATTGG 1758

GTTTCTGAGCATTCAGACTCCGCACCCTCATTTCTAATAAATGCAACATTGGAAAAAAAAAAAAAAAAAAAAAAAAAA 1837

AAAAAAAAAAGGGCGGCCGC 1858

FIG. 31B



·mT281
MAAPAPSLWTLLLLLLLLPPPPGAHGELCRPFGEDNSIPVFCPDFCCGSCSNQYCCSDVL
RKIQWNEEMCPEPESSRFSTPAEETPEHLGSALKFRSSFDSDPMSGFGATVAIGVTIFVV
FIATIIICFTCSCCCLYKMCCPQRPVVTNTTTTTVVHAPYPQPQPQPVAPSYPGPTYQGY
HPMPPPARNASSTLPNAVPTTLPGPAHRAATLP

FIG. 32

```
ALIGN calculates a global alignment of two sequences
 version 2.0uPlease cite: Myers and Miller, CABIOS (1989)
> hT281 a.a.                                               245 aa vs.
> mT281 a.a.                                               213 aa
scoring matrix: pam120.mat, gap penalties: -12/-4
66.5% identity;          Global alignment score: 739

               10        20        30        40        50        60        70
inputs MRLFVRPSVRPAMAAPAPSPWTLSLLLLLLLPSPGAHGELCRPFGEDNSIPESCPDFCCGSCSSQYCCSD
       :            :::::: ::: :::::: :.:::::::::::::::::::  :::::::::.::::::
       M------------AAPAPSLWTLLLLLLLLPPPPGAHGELCRPFGEDNSIPVFCPDFCCGSCSNQYCCSD
                              10        20        30        40        50

               80        90       100       110       120       130
inputs VLKKIQWNEEMCPEPESSRFSAHPE-TPEQLGSALKYQSSLDSDNMPGFGATVAIGLTVFVVFIATIIVC
       ::.::::::::::::::::::.  .: :::.::::::..::.::: :.:::::::::.:.::::::::.:
       VLRKIQWNEEMCPEPESSRFSTPAEETPEHLGSALKFRSSFDSDPMSGFGATVAIGVTIFVVFIATIIIC
       60        70        80        90       100       110       120

    140       150       160       170         180       190       200
inputs FTCSCCCLYKMCCRPRPVVSNTTTTTVVHTAYPQPQP--VAPSYPGPTYQGYHPMPPQPGMPAAPYPTQY
       ::::::::::::: .::::.:::::::::::..::::::  ::::::::::::::::::           :..
       FTCSCCCLYKMCCPQRPVVTNTTTTTVVHAPYPQPQPQPVAPSYPGPTYQGYHPMPP---------PARN
     130       140       150       160       170       180

       210       220       230       240
inputs PPPYLAQPTGPPAYHETLAGASQPPYNPAYMDPPKAVP
       ... :  :.. :.    ::.:.... .           ..:
       ASSTL--PNAVPT---TLPGPAHRA---------ATLP
     190       200                       210
```

FIG. 33

SEQUENCE LISTING

<110> Millennium Pharmaceuticals, Inc.

<120> SECRETED PROTEINS AND USES THEREOF

<130> 7853-210-228

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<150> 09/336,536
<151> 1999-06-18

<160> 198

<170> PatentIn Ver. 2.0

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<212> DNA
<213> Homo sapiens

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gccatcgggg agccgggagg ggggactgcg agaggacccc ggcgtccggg ctcccggtgc 180
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catggcagcc agggcttgcc gggccgcgat ggccgcgacg gccgcgacgg cgcgcccggg 180
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caccccttgcc cttcgaccgc gtgctggtga acgagcaggg acattacgac gccgtcaccg 420
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tctttgct                                                          728

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<211> 243
<212> PRT
<213> Homo sapiens

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1               5                   10                  15

Pro Pro Leu Asp Asp Asn Lys Ile Pro Ser Leu Cys Pro Gly His Pro
            20                  25                  30

Gly Leu Pro Gly Thr Pro Gly His His Gly Ser Gln Gly Leu Pro Gly
        35                  40                  45

Arg Asp Gly Arg Asp Gly Arg Asp Gly Ala Pro Gly Ala Pro Gly Glu
    50                  55                  60

Lys Gly Glu Gly Gly Arg Pro Gly Leu Pro Gly Pro Arg Gly Asp Pro
65                  70                  75                  80

Gly Pro Arg Gly Glu Ala Gly Pro Ala Gly Pro Thr Gly Pro Ala Gly
                85                  90                  95

Glu Cys Ser Val Pro Pro Arg Ser Ala Phe Ser Ala Lys Arg Ser Glu
            100                 105                 110

Ser Arg Val Pro Pro Pro Ser Asp Ala Pro Leu Pro Phe Asp Arg Val
        115                 120                 125

Leu Val Asn Glu Gln Gly His Tyr Asp Ala Val Thr Gly Lys Phe Thr
    130                 135                 140

Cys Gln Val Pro Gly Val Tyr Tyr Phe Ala Val His Ala Thr Val Tyr
145                 150                 155                 160

Arg Ala Ser Leu Gln Phe Asp Leu Val Lys Asn Gly Glu Ser Ile Ala
                165                 170                 175

Ser Phe Phe Gln Phe Phe Gly Gly Trp Pro Lys Pro Ala Ser Leu Ser
            180                 185                 190

Gly Gly Ala Met Val Arg Leu Glu Pro Glu Asp Gln Val Trp Val Gln
        195                 200                 205
```

Val Gly Val Gly Asp Tyr Ile Gly Ile Tyr Ala Ser Ile Lys Thr Asp
    210   215   220

Ser Thr Phe Ser Gly Phe Leu Val Tyr Ser Asp Trp His Ser Ser Pro
225   230   235   240

Val Phe Ala

<210> 4
<211> 228
<212> PRT
<213> Homo sapiens

<400> 4
Ser Pro Pro Leu Asp Asp Asn Lys Ile Pro Ser Leu Cys Pro Gly His
  1   5   10   15

Pro Gly Leu Pro Gly Thr Pro Gly His His Gly Ser Gln Gly Leu Pro
             20   25   30

Gly Arg Asp Gly Arg Asp Gly Arg Asp Gly Ala Pro Gly Ala Pro Gly
         35   40   45

Glu Lys Gly Glu Gly Gly Arg Pro Gly Leu Pro Gly Pro Arg Gly Asp
     50   55   60

Pro Gly Pro Arg Gly Glu Ala Gly Pro Ala Gly Pro Thr Gly Pro Ala
 65   70   75   80

Gly Glu Cys Ser Val Pro Pro Arg Ser Ala Phe Ser Ala Lys Arg Ser
                 85   90   95

Glu Ser Arg Val Pro Pro Pro Ser Asp Ala Pro Leu Pro Phe Asp Arg
            100   105   110

Val Leu Val Asn Glu Gln Gly His Tyr Asp Ala Val Thr Gly Lys Phe
        115   120   125

Thr Cys Gln Val Pro Gly Val Tyr Tyr Phe Ala Val His Ala Thr Val
    130   135   140

Tyr Arg Ala Ser Leu Gln Phe Asp Leu Val Lys Asn Gly Glu Ser Ile
145   150   155   160

Ala Ser Phe Phe Gln Phe Phe Gly Gly Trp Pro Lys Pro Ala Ser Leu
                165   170   175

Ser Gly Gly Ala Met Val Arg Leu Glu Pro Glu Asp Gln Val Trp Val
            180   185   190

Gln Val Gly Val Gly Asp Tyr Ile Gly Ile Tyr Ala Ser Ile Lys Thr
        195   200   205

Asp Ser Thr Phe Ser Gly Phe Leu Val Tyr Ser Asp Trp His Ser Ser
    210   215   220

Pro Val Phe Ala
225

<210> 5
<211> 15
<212> PRT
<213> Homo sapiens

<400> 5
Met Arg Pro Leu Leu Val Leu Leu Leu Leu Gly Leu Ala Ala Gly
1 5 10 15

<210> 6
<211> 60
<212> PRT
<213> Homo sapiens

<400> 6
Gly Thr Pro Gly His His Gly Ser Gln Gly Leu Pro Gly Arg Asp Gly
1 5 10 15

Arg Asp Gly Arg Asp Gly Ala Pro Gly Ala Pro Gly Glu Lys Gly Glu
20 25 30

Gly Gly Arg Pro Gly Leu Pro Gly Pro Arg Gly Asp Pro Gly Pro Arg
35 40 45

Gly Glu Ala Gly Pro Ala Gly Pro Thr Gly Pro Ala
50 55 60

<210> 7
<211> 128
<212> PRT
<213> Homo sapiens

<400> 7
Ala Phe Ser Ala Lys Arg Ser Glu Ser Arg Val Pro Pro Pro Ser Asp
1 5 10 15

Ala Pro Leu Pro Phe Asp Arg Val Leu Val Asn Glu Gln Gly His Tyr
20 25 30

Asp Ala Val Thr Gly Lys Phe Thr Cys Gln Val Pro Gly Val Tyr Tyr
35 40 45

Phe Ala Val His Ala Thr Val Tyr Arg Ala Ser Leu Gln Phe Asp Leu
50 55 60

Val Lys Asn Gly Glu Ser Ile Ala Ser Phe Phe Gln Phe Phe Gly Gly
65 70 75 80

Trp Pro Lys Pro Ala Ser Leu Ser Gly Gly Ala Met Val Arg Leu Glu
85 90 95

Pro Glu Asp Gln Val Trp Val Gln Val Gly Val Gly Asp Tyr Ile Gly

```
        100                 105                 110

Ile Tyr Ala Ser Ile Lys Thr Asp Ser Thr Phe Ser Gly Phe Leu Val
        115                 120                 125
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<210> 8
<211> 1263
<212> DNA
<213> Mus musculus

<400> 8
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gtcgacccac gcgtccgcgc tgtgaagcca gcaaggagca accagaagct aggagtcagt 60
cagcaaggac aggggctgcc tgcctacaga ctacaagaga ggttcctgga gtctgagcct 120
ccggggtcac caccatgagg ccacttcttg cccttctgct tctgggtctg gtgtcaggct 180
ctcctcctct ggacgacaac aagatcccca gcctgtgtcc cgggcagccc ggccttccag 240
gcacaccagg tcaccatggc agccaaggcc tgcctggccg tgacggccgt gatggccgcg 300
acggtgcacc cggagctccg ggagagaaag gcgagggcgg gagaccggga ctacctggcc 360
cacgtgggga gcccgggccg cgtggagagg cagggcccat gggggctatc gggcctgcgg 420
gggagtgctc ggtacccccca cgatcagcct tcagtgccaa gcgatccgag agccgggtac 480
ctccgccagc cgacacaccc ctacctttcg accgtgtgct gctaaatgag cagggccatt 540
acgaccccac tactggcaag ttcacctgcc aagtgcctgg cgtctactac tttgctgtgc 600
acgccactgt ctaccgggcc agcttgcagt ttgatcttgt caaaaacggg cagtccatcg 660
cctctttctt ccagtatttt gggggggtggc ccaagccagc ctcgctctca gggggtgcga 720
tggtaaggct agaacctgag gaccaggtgt gggtgcaggt gggcgtgggt gattacattg 780
gcatctatgc cagcatcaag acagacagta ccttctctgg atttctcgtc tattctgact 840
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agtggagggt gtgacactaa cccgcgcagc gcataccagg agggctggcc ccctggaata 960
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agaatgcagt aggctggcag ctgtgggtcc tggcccagga ctccaaggtg ggatgctcca 1140
ttcctagtcc tgtgtcccct ctaggtccct gactccatct ctgctgctcc cagggcaggc 1200
ctttttctca gaggtcactt aataaaccta aaatcctcaa aaaaaaaaaa aaagggcggc 1260
cgc                                                               1263
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<210> 9
<211> 729
<212> DNA
<213> Mus musculus

<400> 9
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gacaacaaga tccccagcct gtgtcccggg cagcccggcc ttccaggcac accaggtcac 120
catggcagcc aaggcctgcc tggccgtgac ggccgtgatg gccgcgacgg tgcacccgga 180
gctccgggag agaaaggcga gggcgggaga ccgggactac ctggcccacg tggggagccc 240
gggccgcgtg gagaggcagg gcccatgggg gctatcgggc ctgcgggggga gtgctcggta 300
cccccacgat cagccttcag tgccaagcga tccgagagcc gggtacctcc gccagccgac 360
acacccctac ctttcgaccg tgtgctgcta aatgagcagg gccattacga ccccactact 420
ggcaagttca cctgccaagt gcctggcgtc tactactttg ctgtgcacgc cactgtctac 480
cgggccagct tgcagtttga tcttgtcaaa aacgggcagt ccatcgcctc tttcttccag 540
tattttgggg ggtggcccaa gccagcctcg ctctcagggg gtgcgatggt aaggctagaa 600
cctgaggacc aggtgtgggt gcaggtgggc gtgggtgatt acattggcat ctatgccagc 660
atcaagacag acagtacctt ctctggattt ctcgtctatt ctgactggca cagctcccca 720
gtcttcgct                                                         729
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<210> 10
<211> 243
<212> PRT
<213> Mus musculus

<400> 10
Met Arg Pro Leu Leu Ala Leu Leu Leu Leu Gly Leu Val Ser Gly Ser
1 5 10 15

Pro Pro Leu Asp Asp Asn Lys Ile Pro Ser Leu Cys Pro Gly Gln Pro
20 25 30

Gly Leu Pro Gly Thr Pro Gly His His Gly Ser Gln Gly Leu Pro Gly
35 40 45

Arg Asp Gly Arg Asp Gly Arg Asp Gly Ala Pro Gly Ala Pro Gly Glu
50 55 60

Lys Gly Glu Gly Gly Arg Pro Gly Leu Pro Gly Pro Arg Gly Glu Pro
65 70 75 80

Gly Pro Arg Gly Glu Ala Gly Pro Met Gly Ala Ile Gly Pro Ala Gly
85 90 95

Glu Cys Ser Val Pro Pro Arg Ser Ala Phe Ser Ala Lys Arg Ser Glu
100 105 110

Ser Arg Val Pro Pro Pro Ala Asp Thr Pro Leu Pro Phe Asp Arg Val
115 120 125

Leu Leu Asn Glu Gln Gly His Tyr Asp Pro Thr Thr Gly Lys Phe Thr
130 135 140

Cys Gln Val Pro Gly Val Tyr Tyr Phe Ala Val His Ala Thr Val Tyr
145 150 155 160

Arg Ala Ser Leu Gln Phe Asp Leu Val Lys Asn Gly Gln Ser Ile Ala
165 170 175

Ser Phe Phe Gln Tyr Phe Gly Gly Trp Pro Lys Pro Ala Ser Leu Ser
180 185 190

Gly Gly Ala Met Val Arg Leu Glu Pro Glu Asp Gln Val Trp Val Gln
195 200 205

Val Gly Val Gly Asp Tyr Ile Gly Ile Tyr Ala Ser Ile Lys Thr Asp
210 215 220

Ser Thr Phe Ser Gly Phe Leu Val Tyr Ser Asp Trp His Ser Ser Pro
225 230 235 240

Val Phe Ala

<210> 11
<211> 228
<212> PRT
<213> Mus musculus

<400> 11
Ser Pro Pro Leu Asp Asp Asn Lys Ile Pro Ser Leu Cys Pro Gly Gln
1 5 10 15

Pro Gly Leu Pro Gly Thr Pro Gly His His Gly Ser Gln Gly Leu Pro
20 25 30

Gly Arg Asp Gly Arg Asp Gly Arg Asp Gly Ala Pro Gly Ala Pro Gly
35 40 45

Glu Lys Gly Glu Gly Gly Arg Pro Gly Leu Pro Gly Pro Arg Gly Glu
50 55 60

Pro Gly Pro Arg Gly Glu Ala Gly Pro Met Gly Ala Ile Gly Pro Ala
65 70 75 80

Gly Glu Cys Ser Val Pro Pro Arg Ser Ala Phe Ser Ala Lys Arg Ser
85 90 95

Glu Ser Arg Val Pro Pro Pro Ala Asp Thr Pro Leu Pro Phe Asp Arg
100 105 110

Val Leu Leu Asn Glu Gln Gly His Tyr Asp Pro Thr Thr Gly Lys Phe
115 120 125

Thr Cys Gln Val Pro Gly Val Tyr Tyr Phe Ala Val His Ala Thr Val
130 135 140

Tyr Arg Ala Ser Leu Gln Phe Asp Leu Val Lys Asn Gly Gln Ser Ile
145 150 155 160

Ala Ser Phe Phe Gln Tyr Phe Gly Gly Trp Pro Lys Pro Ala Ser Leu
165 170 175

Ser Gly Gly Ala Met Val Arg Leu Glu Pro Glu Asp Gln Val Trp Val
180 185 190

Gln Val Gly Val Gly Asp Tyr Ile Gly Ile Tyr Ala Ser Ile Lys Thr
195 200 205

Asp Ser Thr Phe Ser Gly Phe Leu Val Tyr Ser Asp Trp His Ser Ser
210 215 220

Pro Val Phe Ala
225

<210> 12
<211> 15
<212> PRT
<213> Mus musculus

<400> 12
Met Arg Pro Leu Leu Ala Leu Leu Leu Leu Gly Leu Val Ser Gly
1 5 10 15

<210> 13
<211> 60
<212> PRT
<213> Mus musculus

<400> 13
Gly Thr Pro Gly His His Gly Ser Gln Gly Leu Pro Gly Arg Asp Gly
1 5 10 15

Arg Asp Gly Arg Asp Gly Ala Pro Gly Ala Pro Gly Glu Lys Gly Glu
20 25 30

Gly Gly Arg Pro Gly Leu Pro Gly Pro Arg Gly Glu Pro Gly Pro Arg
35 40 45

Gly Glu Ala Gly Pro Met Gly Ala Ile Gly Pro Ala
50 55 60

<210> 14
<211> 128
<212> PRT
<213> Mus musculus

<400> 14
Ala Phe Ser Ala Lys Arg Ser Glu Ser Arg Val Pro Pro Pro Ala Asp
1 5 10 15

Thr Pro Leu Pro Phe Asp Arg Val Leu Leu Asn Glu Gln Gly His Tyr
20 25 30

Asp Pro Thr Thr Gly Lys Phe Thr Cys Gln Val Pro Gly Val Tyr Tyr
35 40 45

Phe Ala Val His Ala Thr Val Tyr Arg Ala Ser Leu Gln Phe Asp Leu
50 55 60

Val Lys Asn Gly Gln Ser Ile Ala Ser Phe Phe Gln Tyr Phe Gly Gly
65 70 75 80

Trp Pro Lys Pro Ala Ser Leu Ser Gly Gly Ala Met Val Arg Leu Glu
85 90 95

Pro Glu Asp Gln Val Trp Val Gln Val Gly Val Gly Asp Tyr Ile Gly
100 105 110

Ile Tyr Ala Ser Ile Lys Thr Asp Ser Thr Phe Ser Gly Phe Leu Val
115 120 125

<210> 15
<211> 1831
<212> DNA
<213> Homo sapiens

<400> 15
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cttttgtcat ggtcgggacc cctccaagga cagcagcacc accttgtgga gtacatggaa 180
cgccgactag ctgctttaga ggaacggctg gcccagtgcc aggaccagag tagtcggcat 240
gctgctgagc tgcgggactt caagaacaag atgctgccac tgctggaggt ggcagagaag 300
gagcgggagg cactcagaac tgaggccgac accatctccg ggagagtgga tcgtctggag 360
cgggaggtag actatctgga gacccagaac ccagctctgc cctgtgtaga gtttgatgag 420

aaggtgactg gaggccctgg gaccaaaggc aagggaagaa ggaatgagaa gtacgatatg 480
gtgacagact gtggctacac aatctctcaa gtgagatcaa tgaagattct gaagcgattt 540
ggtggcccag ctggtctatg gaccaaggat ccactggggc aaacagagaa gatctacgtg 600
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cagctggtat atggtggctt tctttatttt gctcggaggc ctcctggaag acctggtgga 780
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acctacatcg acctggcagc tgatgaggaa ggtctttggg ctgtctatgc cacccgggag 960
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aatcaaattc tttcagctcc tttgtttcat acggaactcc agatcctgag taatcctttt 1500
agagcccgaa gagtcaaaac cctcaatgtt ccctcctgct ctcctgcccc atgtcaacaa 1560
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gagcaggcag cagtgttctt cccctcagag tgacttgggg agggagaaat aggaggagac 1680
gtccagctct gtcctctctt cctcactcct cccttcagtg tcctgaggaa caggactttc 1740
tccacattgt tttgtattgc aacattttgc attaaaagga aaatccactg ctaaaaaaaa 1800
aaaaaaaaaa aaaaaaaaaa agggcggccg c 1831

<210> 16
<211> 1218
<212> DNA
<213> Homo sapiens

<400> 16
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ggacagcagc accaccttgt ggagtacatg gaacgccgac tagctgcttt agaggaacgg 120
ctggcccagt gccaggacca gagtagtcgg catgctgctg agctgcggga cttcaagaac 180
aagatgctgc cactgctgga ggtggcagag aaggagcggg aggcactcag aactgaggcc 240
gacaccatct ccgggagagt ggatcgtctg gagcgggagg tagactatct ggagacccag 300
aacccagctc tgccctgtgt agagtttgat gagaaggtga ctggaggccc tgggaccaaa 360
ggcaagggaa gaaggaatga gaagtacgat atggtgacag actgtggcta cacaatctct 420
caagtgagat caatgaagat tctgaagcga tttggtggcc cagctggtct atggaccaag 480
gatccactgg ggcaaacaga gaagatctac gtgttagatg ggacacagaa tgacacagcc 540
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gtccgggtgc ccttcccctg ggtaggcaca gggcagctgg tatatggtgg ctttctttat 660
tttgctcgga ggcctcctgg aagacctggt ggaggtggtg agatggagaa cactttgcag 720
ctaatcaaat tccacctggc aaaccgaaca gtggtggaca gctcagtatt cccagcagag 780
gggctgatcc ccccctacgg cttgacagca gacacctaca tcgacctggc agctgatgag 840
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ttagatccac agacactgga cacagagcag cagtgggaca caccatgtcc cagagagaat 960
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aagaaagagg aggaggtt 1218

<210> 17
<211> 406
<212> PRT
<213> Homo sapiens

<400> 17

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Met Gly Pro Ser Thr Pro Leu Leu Ile Leu Phe Leu Leu Ser Trp Ser
  1               5                  10                  15

Gly Pro Leu Gln Gly Gln Gln His His Leu Val Glu Tyr Met Glu Arg
             20                  25                  30

Arg Leu Ala Ala Leu Glu Glu Arg Leu Ala Gln Cys Gln Asp Gln Ser
         35                  40                  45

Ser Arg His Ala Ala Glu Leu Arg Asp Phe Lys Asn Lys Met Leu Pro
     50                  55                  60

Leu Leu Glu Val Ala Glu Lys Glu Arg Glu Ala Leu Arg Thr Glu Ala
 65                  70                  75                  80

Asp Thr Ile Ser Gly Arg Val Asp Arg Leu Glu Arg Glu Val Asp Tyr
                 85                  90                  95

Leu Glu Thr Gln Asn Pro Ala Leu Pro Cys Val Glu Phe Asp Glu Lys
            100                 105                 110

Val Thr Gly Gly Pro Gly Thr Lys Gly Lys Gly Arg Arg Asn Glu Lys
        115                 120                 125

Tyr Asp Met Val Thr Asp Cys Gly Tyr Thr Ile Ser Gln Val Arg Ser
    130                 135                 140

Met Lys Ile Leu Lys Arg Phe Gly Gly Pro Ala Gly Leu Trp Thr Lys
145                 150                 155                 160

Asp Pro Leu Gly Gln Thr Glu Lys Ile Tyr Val Leu Asp Gly Thr Gln
                165                 170                 175

Asn Asp Thr Ala Phe Val Phe Pro Arg Leu Arg Asp Phe Thr Leu Ala
            180                 185                 190

Met Ala Ala Arg Lys Ala Ser Arg Val Arg Val Pro Phe Pro Trp Val
        195                 200                 205

Gly Thr Gly Gln Leu Val Tyr Gly Gly Phe Leu Tyr Phe Ala Arg Arg
    210                 215                 220

Pro Pro Gly Arg Pro Gly Gly Gly Gly Glu Met Glu Asn Thr Leu Gln
225                 230                 235                 240

Leu Ile Lys Phe His Leu Ala Asn Arg Thr Val Val Asp Ser Ser Val
                245                 250                 255

Phe Pro Ala Glu Gly Leu Ile Pro Pro Tyr Gly Leu Thr Ala Asp Thr
            260                 265                 270

Tyr Ile Asp Leu Ala Ala Asp Glu Glu Gly Leu Trp Ala Val Tyr Ala
        275                 280                 285

Thr Arg Glu Asp Asp Arg His Leu Cys Leu Ala Lys Leu Asp Pro Gln
    290                 295                 300
```

Thr Leu Asp Thr Glu Gln Gln Trp Asp Thr Pro Cys Pro Arg Glu Asn
305 310 315 320

Ala Glu Ala Ala Phe Val Ile Cys Gly Thr Leu Tyr Val Val Tyr Asn
325 330 335

Thr Arg Pro Ala Ser Arg Ala Arg Ile Gln Cys Ser Phe Asp Ala Ser
340 345 350

Gly Thr Leu Thr Pro Glu Arg Ala Ala Leu Pro Tyr Phe Pro Arg Arg
355 360 365

Tyr Gly Ala His Ala Ser Leu Arg Tyr Asn Pro Arg Glu Arg Gln Leu
370 375 380

Tyr Ala Trp Asp Asp Gly Tyr Gln Ile Val Tyr Lys Leu Glu Met Arg
385 390 395 400

Lys Lys Glu Glu Glu Val
405

<210> 18
<211> 385
<212> PRT
<213> Homo sapiens

<400> 18
Gln Gln His His Leu Val Glu Tyr Met Glu Arg Arg Leu Ala Ala Leu
1 5 10 15

Glu Glu Arg Leu Ala Gln Cys Gln Asp Gln Ser Ser Arg His Ala Ala
20 25 30

Glu Leu Arg Asp Phe Lys Asn Lys Met Leu Pro Leu Leu Glu Val Ala
35 40 45

Glu Lys Glu Arg Glu Ala Leu Arg Thr Glu Ala Asp Thr Ile Ser Gly
50 55 60

Arg Val Asp Arg Leu Glu Arg Glu Val Asp Tyr Leu Glu Thr Gln Asn
65 70 75 80

Pro Ala Leu Pro Cys Val Glu Phe Asp Glu Lys Val Thr Gly Gly Pro
85 90 95

Gly Thr Lys Gly Lys Gly Arg Arg Asn Glu Lys Tyr Asp Met Val Thr
100 105 110

Asp Cys Gly Tyr Thr Ile Ser Gln Val Arg Ser Met Lys Ile Leu Lys
115 120 125

Arg Phe Gly Gly Pro Ala Gly Leu Trp Thr Lys Asp Pro Leu Gly Gln
130 135 140

Thr Glu Lys Ile Tyr Val Leu Asp Gly Thr Gln Asn Asp Thr Ala Phe
145 150 155 160

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Val Phe Pro Arg Leu Arg Asp Phe Thr Leu Ala Met Ala Ala Arg Lys
                165                 170                 175

Ala Ser Arg Val Arg Val Pro Phe Pro Trp Val Gly Thr Gly Gln Leu
            180                 185                 190

Val Tyr Gly Gly Phe Leu Tyr Phe Ala Arg Arg Pro Pro Gly Arg Pro
        195                 200                 205

Gly Gly Gly Gly Glu Met Glu Asn Thr Leu Gln Leu Ile Lys Phe His
    210                 215                 220

Leu Ala Asn Arg Thr Val Val Asp Ser Ser Val Phe Pro Ala Glu Gly
225                 230                 235                 240

Leu Ile Pro Pro Tyr Gly Leu Thr Ala Asp Thr Tyr Ile Asp Leu Ala
                245                 250                 255

Ala Asp Glu Glu Gly Leu Trp Ala Val Tyr Ala Thr Arg Glu Asp Asp
            260                 265                 270

Arg His Leu Cys Leu Ala Lys Leu Asp Pro Gln Thr Leu Asp Thr Glu
        275                 280                 285

Gln Gln Trp Asp Thr Pro Cys Pro Arg Glu Asn Ala Glu Ala Ala Phe
    290                 295                 300

Val Ile Cys Gly Thr Leu Tyr Val Val Tyr Asn Thr Arg Pro Ala Ser
305                 310                 315                 320

Arg Ala Arg Ile Gln Cys Ser Phe Asp Ala Ser Gly Thr Leu Thr Pro
                325                 330                 335

Glu Arg Ala Ala Leu Pro Tyr Phe Pro Arg Arg Tyr Gly Ala His Ala
            340                 345                 350

Ser Leu Arg Tyr Asn Pro Arg Glu Arg Gln Leu Tyr Ala Trp Asp Asp
        355                 360                 365

Gly Tyr Gln Ile Val Tyr Lys Leu Glu Met Arg Lys Lys Glu Glu Glu
    370                 375                 380

Val
385


<210> 19
<211> 21
<212> PRT
<213> Homo sapiens

<400> 19
Met Gly Pro Ser Thr Pro Leu Leu Ile Leu Phe Leu Leu Ser Trp Ser
  1               5                  10                  15

Gly Pro Leu Gln Gly
            20
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<210> 20
<211> 244
<212> PRT
<213> Homo sapiens

<400> 20
Met Leu Leu Leu Gly Ala Val Leu Leu Leu Leu Ala Leu Pro Gly His
1 5 10 15

Asp Gln Glu Thr Thr Thr Gln Gly Pro Gly Val Leu Leu Pro Leu Pro
20 25 30

Lys Gly Ala Cys Thr Gly Trp Met Ala Gly Ile Pro Gly His Pro Gly
35 40 45

His Asn Gly Ala Pro Gly Arg Asp Gly Arg Asp Gly Thr Pro Gly Glu
50 55 60

Lys Gly Glu Lys Gly Asp Pro Gly Leu Ile Gly Pro Lys Gly Asp Ile
65 70 75 80

Gly Glu Thr Gly Val Pro Gly Ala Glu Gly Pro Arg Gly Phe Pro Gly
85 90 95

Ile Gln Gly Arg Lys Gly Glu Pro Gly Glu Gly Ala Tyr Val Tyr Arg
100 105 110

Ser Ala Phe Ser Val Gly Leu Glu Thr Tyr Val Thr Ile Pro Asn Met
115 120 125

Pro Ile Arg Phe Thr Lys Ile Phe Tyr Asn Gln Gln Asn His Tyr Asp
130 135 140

Gly Ser Thr Gly Lys Phe His Cys Asn Ile Pro Gly Leu Tyr Tyr Phe
145 150 155 160

Ala Tyr His Ile Thr Val Tyr Met Lys Asp Val Lys Val Ser Leu Phe
165 170 175

Lys Lys Asp Lys Ala Met Leu Phe Thr Tyr Asp Gln Tyr Gln Glu Asn
180 185 190

Asn Val Asp Gln Ala Ser Gly Ser Val Leu Leu His Leu Glu Val Gly
195 200 205

Asp Gln Val Trp Leu Gln Val Tyr Gly Glu Gly Glu Arg Asn Gly Leu
210 215 220

Tyr Ala Asp Asn Asp Asn Asp Ser Thr Phe Thr Gly Phe Leu Leu Tyr
225 230 235 240

His Asp Thr Asn

<210> 21
<211> 1721
<212> DNA

<213> Mus musculus

<400> 21
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gaacgccgac tagctgcctt agaggaacgg ctggcccaat gccaggatca gagtagtcgg 180
catgctgccg agcttcggga cttcaaaaac aagatgttgc ctctcctgga ggtggcagag 240
aaggagcggg agaccctcag aactgaagca gactccatct caggaagagt ggaccgtctt 300
gaaagggagg tagactatct ggagacacag aacccagctt tgccctgtgt agagctggat 360
gagaaggtga ctggaggtcc tggagccaaa ggcaagggcc gaagaaatga gaaatacgat 420
atggtgacgg actgtagcta cacagtcgct caggtgaggt caatgaagat cctgaagcgg 480
tttggtggtt cagttggcct atggaccaag gatccgctgg ggccagcaga gaagatctac 540
gtgttagacg gcacccagaa cgacacggct tttgtcttcc caaggctgcg tgacttcacc 600
cttgccatgg ctgcccggaa agcttcccga attcgggtgc ccttcccctg ggtaggcacg 660
gggcagctgg tgtacggtgg cttcctttat tatgctcgaa ggcctcctgg aggacctgga 720
gggggtggtg aattggagaa cactctgcag ctgatcaaat ttcacttggc aaaccgaaca 780
gtggtggata gctcagtgtt ccctgcagag agcctgatac ccccctacgg cctgacagca 840
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cagtgggaca caccatgtcc cagagagaac gcagaggctg cgtttgtcat ctgtgggacc 1020
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taccagattg tctacaaatt ggagatgaag aagaaggagg aggaagttta agcagctagc 1260
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tccttcaaaa cgaaggccag tggtggtagc tcatataccc taatttctaa aggacaacca 1380
aattctcaag cccctctgtt ttatgcagaa ctccagatcc tgggtagcat tttagaactg 1440
aacagcaaac aaacacccta aatcttcact cctgccttat gtccacaaag tttagttcca 1500
aactcagagc cctgtccttt ggagagggtc aaccccagac agcaggcgac agcattcttg 1560
ccctcagtat gaccgaaggg agagaactca gagacaaagc tgccctccct cccttccccc 1620
tccagtgtag ggagaatggg ggctttcccc acatcacttt gtatggtaac agtttgcatt 1680
aaaaggaaaa cccaccaaaa aaaaaaaaaa agggcggccg c 1721

<210> 22
<211> 1218
<212> DNA
<213> Mus musculus

<400> 22
atggggccca gtgctcctct gctgctcctc ttctttttgt catggacggg accccttcag 60
ggacagcagc accaccttgt ggagtacatg gaacgccgac tagctgcctt agaggaacgg 120
ctggcccaat gccaggatca gagtagtcgg catgctgccg agcttcggga cttcaaaaac 180
aagatgttgc ctctcctgga ggtggcagag aaggagcggg agaccctcag aactgaagca 240
gactccatct caggaagagt ggaccgtctt gaaagggagg tagactatct ggagacacag 300
aacccagctt tgccctgtgt agagctggat gagaaggtga ctggaggtcc tggagccaaa 360
ggcaagggcc gaagaaatga gaaatacgat atggtgacgg actgtagcta cacagtcgct 420
caggtgaggt caatgaagat cctgaagcgg tttggtggtt cagttggcct atggaccaag 480
gatccgctgg ggccagcaga gaagatctac gtgttagacg gcacccagaa cgacacggct 540
tttgtcttcc caaggctgcg tgacttcacc cttgccatgg ctgcccggaa agcttcccga 600
attcgggtgc ccttcccctg ggtaggcacg gggcagctgg tgtacggtgg cttcctttat 660
tatgctcgaa ggcctcctgg aggacctgga gggggtggtg aattggagaa cactctgcag 720
ctgatcaaat ttcacttggc aaaccgaaca gtggtggata gctcagtgtt ccctgcagag 780
agcctgatac ccccctacgg cctgacagca gatacatata tcgacctggc agctgatgag 840
gagggcctgt gggctgtcta tgccactcga gatgatgaca ggcatttgtg tctagccaag 900
ttagacccac agacacttga cacagagcag cagtgggaca caccatgtcc cagagagaac 960
gcagaggctg cgtttgtcat ctgtgggacc ctgtacgttg tctataacac ccgccctgcc 1020
agtagggctc gtattcagtg ttccttcgat gccagtggta ctctcgcccc tgaaagggca 1080
gcactctcct attttccacg ccgatatggt gcccatgcca gccttcgcta taacccccgt 1140

gagcgccagc tgtatgcctg ggatgatggc taccagattg tctacaaatt ggagatgaag 1200
aagaaggagg aggaagtt 1218

<210> 23
<211> 406
<212> PRT
<213> Mus musculus

<400> 23
Met Gly Pro Ser Ala Pro Leu Leu Leu Leu Phe Phe Leu Ser Trp Thr
1 5 10 15

Gly Pro Leu Gln Gly Gln Gln His His Leu Val Glu Tyr Met Glu Arg
20 25 30

Arg Leu Ala Ala Leu Glu Glu Arg Leu Ala Gln Cys Gln Asp Gln Ser
35 40 45

Ser Arg His Ala Ala Glu Leu Arg Asp Phe Lys Asn Lys Met Leu Pro
50 55 60

Leu Leu Glu Val Ala Glu Lys Glu Arg Glu Thr Leu Arg Thr Glu Ala
65 70 75 80

Asp Ser Ile Ser Gly Arg Val Asp Arg Leu Glu Arg Glu Val Asp Tyr
85 90 95

Leu Glu Thr Gln Asn Pro Ala Leu Pro Cys Val Glu Leu Asp Glu Lys
100 105 110

Val Thr Gly Gly Pro Gly Ala Lys Gly Lys Gly Arg Arg Asn Glu Lys
115 120 125

Tyr Asp Met Val Thr Asp Cys Ser Tyr Thr Val Ala Gln Val Arg Ser
130 135 140

Met Lys Ile Leu Lys Arg Phe Gly Gly Ser Val Gly Leu Trp Thr Lys
145 150 155 160

Asp Pro Leu Gly Pro Ala Glu Lys Ile Tyr Val Leu Asp Gly Thr Gln
165 170 175

Asn Asp Thr Ala Phe Val Phe Pro Arg Leu Arg Asp Phe Thr Leu Ala
180 185 190

Met Ala Ala Arg Lys Ala Ser Arg Ile Arg Val Pro Phe Pro Trp Val
195 200 205

Gly Thr Gly Gln Leu Val Tyr Gly Gly Phe Leu Tyr Tyr Ala Arg Arg
210 215 220

Pro Pro Gly Gly Pro Gly Gly Gly Gly Glu Leu Glu Asn Thr Leu Gln
225 230 235 240

Leu Ile Lys Phe His Leu Ala Asn Arg Thr Val Val Asp Ser Ser Val
245 250 255

Phe Pro Ala Glu Ser Leu Ile Pro Pro Tyr Gly Leu Thr Ala Asp Thr

260 265 270

Tyr Ile Asp Leu Ala Ala Asp Glu Glu Gly Leu Trp Ala Val Tyr Ala
275 280 285

Thr Arg Asp Asp Asp Arg His Leu Cys Leu Ala Lys Leu Asp Pro Gln
290 295 300

Thr Leu Asp Thr Glu Gln Gln Trp Asp Thr Pro Cys Pro Arg Glu Asn
305 310 315 320

Ala Glu Ala Ala Phe Val Ile Cys Gly Thr Leu Tyr Val Val Tyr Asn
325 330 335

Thr Arg Pro Ala Ser Arg Ala Arg Ile Gln Cys Ser Phe Asp Ala Ser
340 345 350

Gly Thr Leu Ala Pro Glu Arg Ala Ala Leu Ser Tyr Phe Pro Arg Arg
355 360 365

Tyr Gly Ala His Ala Ser Leu Arg Tyr Asn Pro Arg Glu Arg Gln Leu
370 375 380

Tyr Ala Trp Asp Asp Gly Tyr Gln Ile Val Tyr Lys Leu Glu Met Lys
385 390 395 400

Lys Lys Glu Glu Glu Val
405

<210> 24
<211> 385
<212> PRT
<213> Mus musculus

<400> 24
Gln Gln His His Leu Val Glu Tyr Met Glu Arg Arg Leu Ala Ala Leu
1 5 10 15

Glu Glu Arg Leu Ala Gln Cys Gln Asp Gln Ser Ser Arg His Ala Ala
20 25 30

Glu Leu Arg Asp Phe Lys Asn Lys Met Leu Pro Leu Leu Glu Val Ala
35 40 45

Glu Lys Glu Arg Glu Thr Leu Arg Thr Glu Ala Asp Ser Ile Ser Gly
50 55 60

Arg Val Asp Arg Leu Glu Arg Glu Val Asp Tyr Leu Glu Thr Gln Asn
65 70 75 80

Pro Ala Leu Pro Cys Val Glu Leu Asp Glu Lys Val Thr Gly Gly Pro
85 90 95

Gly Ala Lys Gly Lys Gly Arg Arg Asn Glu Lys Tyr Asp Met Val Thr
100 105 110

Asp Cys Ser Tyr Thr Val Ala Gln Val Arg Ser Met Lys Ile Leu Lys

115 120 125

Arg Phe Gly Gly Ser Val Gly Leu Trp Thr Lys Asp Pro Leu Gly Pro
130 135 140

Ala Glu Lys Ile Tyr Val Leu Asp Gly Thr Gln Asn Asp Thr Ala Phe
145 150 155 160

Val Phe Pro Arg Leu Arg Asp Phe Thr Leu Ala Met Ala Ala Arg Lys
165 170 175

Ala Ser Arg Ile Arg Val Pro Phe Pro Trp Val Gly Thr Gly Gln Leu
180 185 190

Val Tyr Gly Gly Phe Leu Tyr Tyr Ala Arg Arg Pro Pro Gly Gly Pro
195 200 205

Gly Gly Gly Gly Glu Leu Glu Asn Thr Leu Gln Leu Ile Lys Phe His
210 215 220

Leu Ala Asn Arg Thr Val Val Asp Ser Ser Val Phe Pro Ala Glu Ser
225 230 235 240

Leu Ile Pro Pro Tyr Gly Leu Thr Ala Asp Thr Tyr Ile Asp Leu Ala
245 250 255

Ala Asp Glu Glu Gly Leu Trp Ala Val Tyr Ala Thr Arg Asp Asp Asp
260 265 270

Arg His Leu Cys Leu Ala Lys Leu Asp Pro Gln Thr Leu Asp Thr Glu
275 280 285

Gln Gln Trp Asp Thr Pro Cys Pro Arg Glu Asn Ala Glu Ala Ala Phe
290 295 300

Val Ile Cys Gly Thr Leu Tyr Val Val Tyr Asn Thr Arg Pro Ala Ser
305 310 315 320

Arg Ala Arg Ile Gln Cys Ser Phe Asp Ala Ser Gly Thr Leu Ala Pro
325 330 335

Glu Arg Ala Ala Leu Ser Tyr Phe Pro Arg Arg Tyr Gly Ala His Ala
340 345 350

Ser Leu Arg Tyr Asn Pro Arg Glu Arg Gln Leu Tyr Ala Trp Asp Asp
355 360 365

Gly Tyr Gln Ile Val Tyr Lys Leu Glu Met Lys Lys Lys Glu Glu Glu
370 375 380

Val
385

<210> 25
<211> 21
<212> PRT
<213> Mus musculus

<400> 25
Met Gly Pro Ser Ala Pro Leu Leu Leu Leu Phe Phe Leu Ser Trp Thr
1 5 10 15

Gly Pro Leu Gln Gly
20

<210> 26
<211> 1869
<212> DNA
<213> Homo sapiens

<220>
<221> modified_base
<222> all "n" positions
<223> n=a, c, g, or t

<400> 26
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gcgcacgctc cggccgtcgc gcagcctcgg cacctgcagg tccgtgcgtc ccgcggctgg 120
cgcccctgac tccgtcccgg ccagggaggg ccatgatttc cctcccgggg cccctggtga 180
ccaacttgnt gcggtttttg ttcctggggc tgagtgccct cgcgcccccc tcgcgggccc 240
agctgcaact gcacttgccc gccaaccggt tgcaggcggt ggaggagggg gaaagtggtg 300
cttcagcatg gtacaccttg cacagggagg tgtcttcatc ccagccatgg gaggtgccct 360
ttgtgatgtg gttcttcaaa cagaaagaaa aggaggatca ggtgttgtcc tacatcaatg 420
gggtcacaac aagcaaacct ggagtatcct tggtctactc catgccctcc cggaacctgt 480
ccctgcgggt ggagggtctc caggagaaag actctggccc ctacagctgc tccgtgaatg 540
tgcaagacaa acaaggcaaa tctaggggcc acagcatcaa aaccttagaa ctcaatgtac 600
tggttcctcc agctcctcca tcctgccgtc tccagggtgt gccccatgtg gggcaaacg 660
tgaccctgag ctgccagtct ccaaggagta agcccgctgt ccaataccag tgggatcggc 720
agcttccatc cttccagact ttctttgcac cagcattaga tgtcatccgt gggtctttaa 780
gcctcaccaa cctttcgtct tccatggctg gagtctatgt ctgcaaggcc cacaatgagg 840
tgggcactgc ccaatgtaat gtgacgctgg aagtgagcac agggcctgga gctgcagtgg 900
ttgctgaagc tgttgtgggt accctggttg gactggggtt gctggctggg ctggtcctct 960
tgtaccaccg ccggggcaag gccctggagg agccagccaa tgatatcaag gaggatgcca 1020
ttgctccccg gaccctgccc tggcccaaga gctcagacac aatctccaag aatgggaccc 1080
tttcctctgt cacctccgca cgagccctcc ggccacccca tggccctccc aggcctggtg 1140
cattgacccc cacgcccagt ctatccagcc aggccctgcc ctcaccaaga catgcccacg 1200
acagatgggg cccaccctca accaatatcc cccatccctg gtggggtttt ttcctttggc 1260
tttgagccgc atgggtgctg ngcctgtgat ggngcctgcc cagagtcaag ctggctctct 1320
ggtatgatga ccccaccact cattggctaa aggatttggg gtctctcctt cctataaggg 1380
tcacctctag cacagaggcc tgagtcatgg gaaagagtca cactcctgac ccttagtact 1440
ctgcccccac ctctctttac tgtgggaaaa ccatctcagt aagacctaag tgtccaggag 1500
acagaaggag aagaggaagt ggatctggaa ttgggaggag cctccaccca cccctgactc 1560
ctccttatga agccagctgc tgaaattagc tactcaccaa gagtgagggg cagagacttc 1620
cagtcactga gtctcccagg ccccccttgat ctgtacccca cccctatcta acaccacccct 1680
tggctcccac tccagctccc tgtattgata taacctgtca ggctggcttg gttaggtttt 1740
actggggcag aggataggga atctcttatt aaaactaaca tgaaatatgt gttgttttca 1800
tttgcaaatt taaataaaga tacataatgt ttgtatgaga taagaaaaaa aaaaaaaaag 1860
ggcggccgc 1869

<210> 27
<211> 1110
<212> DNA
<213> Homo sapiens

<220>

<221> modified_base
<222> all "n" positions
<223> n=a, c, g, or t

<400> 27
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agtgccctcg cgcccccctc gcgggcccag ctgcaactgc acttgcccgc caaccggttg 120
caggcggtgg aggaggggga aagtggtgct tcagcatggt acaccttgca cagggaggtg 180
tcttcatccc agccatggga ggtgcccttt gtgatgtggt tcttcaaaca gaaagaaaag 240
gaggatcagg tgttgtccta catcaatggg gtcacaacaa gcaaacctgg agtatccttg 300
gtctactcca tgccctcccg gaacctgtcc ctgcgggtgg agggtctcca ggagaaagac 360
tctggcccct acagctgctc cgtgaatgtg caagacaaac aaggcaaatc taggggccac 420
agcatcaaaa ccttagaact caatgtactg gttcctccag ctcctccatc ctgccgtctc 480
cagggtgtgc cccatgtggg ggcaaacgtg accctgagct gccagtctcc aaggagtaag 540
cccgctgtcc aataccagtg ggatcggcag cttccatcct tccagacttt ctttgcacca 600
gcattagatg tcatccgtgg gtctttaagc ctcaccaacc tttcgtcttc catggctgga 660
gtctatgtct gcaaggccca caatgaggtg ggcactgccc aatgtaatgt gacgctggaa 720
gtgagcacag ggcctggagc tgcagtggtt gctgaagctg ttgtgggtac cctggttgga 780
ctggggttgc tggctgggct ggtcctcttg taccaccgcc ggggcaaggc cctggaggag 840
ccagccaatg atatcaagga ggatgccatt gctccccgga ccctgccctg gcccaagagc 900
tcagacacaa tctccaagaa tgggaccctt tcctctgtca cctccgcacg agccctccgg 960
ccaccccatg gccctcccag gcctggtgca ttgaccccca cgcccagtct atccagccag 1020
gccctgccct caccaagaca tgcccacgac agatggggcc caccctcaac caatatcccc 1080
catccctggt ggggtttttt cctttggctt                                  1110
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<210> 28
<211> 370
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (13)
<223> Xaa=unknown amino acid

<400> 28
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Met Ile Ser Leu Pro Gly Pro Leu Val Thr Asn Leu Xaa Arg Phe Leu
  1               5                  10                  15

Phe Leu Gly Leu Ser Ala Leu Ala Pro Pro Ser Arg Ala Gln Leu Gln
             20                  25                  30

Leu His Leu Pro Ala Asn Arg Leu Gln Ala Val Glu Glu Gly Glu Ser
         35                  40                  45

Gly Ala Ser Ala Trp Tyr Thr Leu His Arg Glu Val Ser Ser Ser Gln
     50                  55                  60

Pro Trp Glu Val Pro Phe Val Met Trp Phe Phe Lys Gln Lys Glu Lys
 65                  70                  75                  80

Glu Asp Gln Val Leu Ser Tyr Ile Asn Gly Val Thr Thr Ser Lys Pro
                 85                  90                  95

Gly Val Ser Leu Val Tyr Ser Met Pro Ser Arg Asn Leu Ser Leu Arg
            100                 105                 110

Val Glu Gly Leu Gln Glu Lys Asp Ser Gly Pro Tyr Ser Cys Ser Val
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115 120 125

Asn Val Gln Asp Lys Gln Gly Lys Ser Arg Gly His Ser Ile Lys Thr
130 135 140

Leu Glu Leu Asn Val Leu Val Pro Pro Ala Pro Pro Ser Cys Arg Leu
145 150 155 160

Gln Gly Val Pro His Val Gly Ala Asn Val Thr Leu Ser Cys Gln Ser
165 170 175

Pro Arg Ser Lys Pro Ala Val Gln Tyr Gln Trp Asp Arg Gln Leu Pro
180 185 190

Ser Phe Gln Thr Phe Phe Ala Pro Ala Leu Asp Val Ile Arg Gly Ser
195 200 205

Leu Ser Leu Thr Asn Leu Ser Ser Ser Met Ala Gly Val Tyr Val Cys
210 215 220

Lys Ala His Asn Glu Val Gly Thr Ala Gln Cys Asn Val Thr Leu Glu
225 230 235 240

Val Ser Thr Gly Pro Gly Ala Ala Val Val Ala Glu Ala Val Val Gly
245 250 255

Thr Leu Val Gly Leu Gly Leu Leu Ala Gly Leu Val Leu Leu Tyr His
260 265 270

Arg Arg Gly Lys Ala Leu Glu Glu Pro Ala Asn Asp Ile Lys Glu Asp
275 280 285

Ala Ile Ala Pro Arg Thr Leu Pro Trp Pro Lys Ser Ser Asp Thr Ile
290 295 300

Ser Lys Asn Gly Thr Leu Ser Ser Val Thr Ser Ala Arg Ala Leu Arg
305 310 315 320

Pro Pro His Gly Pro Pro Arg Pro Gly Ala Leu Thr Pro Thr Pro Ser
325 330 335

Leu Ser Ser Gln Ala Leu Pro Ser Pro Arg His Ala His Asp Arg Trp
340 345 350

Gly Pro Pro Ser Thr Asn Ile Pro His Pro Trp Trp Gly Phe Phe Leu
355 360 365

Trp Leu
370

<210> 29
<211> 341
<212> PRT
<213> Mus musculus

<400> 29
Gln Leu Gln Leu His Leu Pro Ala Asn Arg Leu Gln Ala Val Glu Glu

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1               5                   10                  15
Gly Glu Ser Gly Ala Ser Ala Trp Tyr Thr Leu His Arg Glu Val Ser
                20                  25                  30
Ser Ser Gln Pro Trp Glu Val Pro Phe Val Met Trp Phe Phe Lys Gln
            35                  40                  45
Lys Glu Lys Glu Asp Gln Val Leu Ser Tyr Ile Asn Gly Val Thr Thr
        50                  55                  60
Ser Lys Pro Gly Val Ser Leu Val Tyr Ser Met Pro Ser Arg Asn Leu
65                  70                  75                      80
Ser Leu Arg Val Glu Gly Leu Gln Glu Lys Asp Ser Gly Pro Tyr Ser
                85                  90                  95
Cys Ser Val Asn Val Gln Asp Lys Gln Gly Lys Ser Arg Gly His Ser
            100                 105                 110
Ile Lys Thr Leu Glu Leu Asn Val Leu Val Pro Pro Ala Pro Pro Ser
        115                 120                 125
Cys Arg Leu Gln Gly Val Pro His Val Gly Ala Asn Val Thr Leu Ser
    130                 135                 140
Cys Gln Ser Pro Arg Ser Lys Pro Ala Val Gln Tyr Gln Trp Asp Arg
145                 150                 155                     160
Gln Leu Pro Ser Phe Gln Thr Phe Phe Ala Pro Ala Leu Asp Val Ile
                165                 170                 175
Arg Gly Ser Leu Ser Leu Thr Asn Leu Ser Ser Ser Met Ala Gly Val
            180                 185                 190
Tyr Val Cys Lys Ala His Asn Glu Val Gly Thr Ala Gln Cys Asn Val
        195                 200                 205
Thr Leu Glu Val Ser Thr Gly Pro Gly Ala Ala Val Val Ala Glu Ala
    210                 215                 220
Val Val Gly Thr Leu Val Gly Leu Gly Leu Leu Ala Gly Leu Val Leu
225                 230                 235                     240
Leu Tyr His Arg Arg Gly Lys Ala Leu Glu Glu Pro Ala Asn Asp Ile
                245                 250                 255
Lys Glu Asp Ala Ile Ala Pro Arg Thr Leu Pro Trp Pro Lys Ser Ser
            260                 265                 270
Asp Thr Ile Ser Lys Asn Gly Thr Leu Ser Ser Val Thr Ser Ala Arg
        275                 280                 285
Ala Leu Arg Pro Pro His Gly Pro Pro Arg Pro Gly Ala Leu Thr Pro
    290                 295                 300
Thr Pro Ser Leu Ser Ser Gln Ala Leu Pro Ser Pro Arg His Ala His
305                 310                 315                     320
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Asp Arg Trp Gly Pro Pro Ser Thr Asn Ile Pro His Pro Trp Trp Gly
325 330 335

Phe Phe Leu Trp Leu
340

<210> 30
<211> 29
<212> PRT
<213> Mus musculus

<220>
<221> SITE
<222> (13)
<223> Xaa=unknown amino acid
<400> 30

Met Ile Ser Leu Pro Gly Pro Leu Val Thr Asn Leu Xaa Arg Phe Leu
1 5 10 15

Phe Leu Gly Leu Ser Ala Leu Ala Pro Pro Ser Arg Ala
20 25

<210> 31
<211> 246
<212> PRT
<213> Mus musculus

<220>
<221> SITE
<222> (13)
<223> Xaa=unknown amino acid
<400> 31

Met Ile Ser Leu Pro Gly Pro Leu Val Thr Asn Leu Xaa Arg Phe Leu
1 5 10 15

Phe Leu Gly Leu Ser Ala Leu Ala Pro Pro Ser Arg Ala Gln Leu Gln
20 25 30

Leu His Leu Pro Ala Asn Arg Leu Gln Ala Val Glu Glu Gly Glu Ser
35 40 45

Gly Ala Ser Ala Trp Tyr Thr Leu His Arg Glu Val Ser Ser Ser Gln
50 55 60

Pro Trp Glu Val Pro Phe Val Met Trp Phe Phe Lys Gln Lys Glu Lys
65 70 75 80

Glu Asp Gln Val Leu Ser Tyr Ile Asn Gly Val Thr Thr Ser Lys Pro
85 90 95

Gly Val Ser Leu Val Tyr Ser Met Pro Ser Arg Asn Leu Ser Leu Arg
100 105 110

Val Glu Gly Leu Gln Glu Lys Asp Ser Gly Pro Tyr Ser Cys Ser Val

```
        115                 120                 125

Asn Val Gln Asp Lys Gln Gly Lys Ser Arg Gly His Ser Ile Lys Thr
    130                 135                 140

Leu Glu Leu Asn Val Leu Val Pro Pro Ala Pro Pro Ser Cys Arg Leu
145                 150                 155                 160

Gln Gly Val Pro His Val Gly Ala Asn Val Thr Leu Ser Cys Gln Ser
                165                 170                 175

Pro Arg Ser Lys Pro Ala Val Gln Tyr Gln Trp Asp Arg Gln Leu Pro
            180                 185                 190

Ser Phe Gln Thr Phe Phe Ala Pro Ala Leu Asp Val Ile Arg Gly Ser
        195                 200                 205

Leu Ser Leu Thr Asn Leu Ser Ser Ser Met Ala Gly Val Tyr Val Cys
    210                 215                 220

Lys Ala His Asn Glu Val Gly Thr Ala Gln Cys Asn Val Thr Leu Glu
225                 230                 235                 240

Val Ser Thr Gly Pro Gly
                245


<210> 32
<211> 653
<212> DNA
<213> Homo sapiens

<400> 32
tttttgcat gtaactttt tattgaggca caacaaggca ttgtaacttg cctggacttg 60
aggcagtcag tttagtaagc tgaacgttaa tacagttaag gattaagtgc aaacaatata 120
cattcacagc ttgactagcg aggctacatc acaatttata aagtgccaga ttagtgctaa 180
ttgtcattca gcttgatttt tcacctcagg aaggaaaaca aaaaagtaag gacctcctcc 240
ctctaggaac aaaaaacatt ttcctaaacc aatcagtcat gagggcaaag actacttttc 300
cttcaatccc actaattaga acaccatcct tttattgtca atactgtact gactttcaat 360
cttgataaag aagatagcct gaaaacgtag aatatttcca gctacttcca taaattgctc 420
ccctgtgcag acgtaaccat atctggtctc cctggaagag ctgaagaatt gcatgattgc 480
tagcagtttc atggtctgga gcaccatcat tggcataggc tgataccaag acctcttcat 540
tcttcantga ggttgacata cagtggcaca ttcactgcca gcttttacat gtgaaaaatg 600
aaaaacgtag tgccattcac ttggcaatta aatctaccaa agctgagatc aaa        653

<210> 33
<211> 25
<212> PRT
<213> Mus musculus

<400> 33
Ala Ala Val Val Ala Glu Ala Val Val Gly Thr Leu Val Gly Leu Gly
 1               5                  10                  15

Leu Leu Ala Gly Leu Val Leu Leu Tyr
            20                  25
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<210> 34
<211> 99
<212> PRT
<213> Mus musculus

<400> 34
His Arg Arg Gly Lys Ala Leu Glu Glu Pro Ala Asn Asp Ile Lys Glu
1   5   10   15

Asp Ala Ile Ala Pro Arg Thr Leu Pro Trp Pro Lys Ser Ser Asp Thr
            20   25   30

Ile Ser Lys Asn Gly Thr Leu Ser Ser Val Thr Ser Ala Arg Ala Leu
        35   40   45

Arg Pro Pro His Gly Pro Pro Arg Pro Gly Ala Leu Thr Pro Thr Pro
    50   55   60

Ser Leu Ser Ser Gln Ala Leu Pro Ser Pro Arg His Ala His Asp Arg
65   70   75   80

Trp Gly Pro Pro Ser Thr Asn Ile Pro His Pro Trp Trp Gly Phe Phe
                85   90   95

Leu Trp Leu

<210> 35
<211> 80
<212> PRT
<213> Mus musculus

<400> 35
Gly Ala Ser Ala Trp Tyr Thr Leu His Arg Glu Val Ser Ser Ser Gln
1   5   10   15

Pro Trp Glu Val Pro Phe Val Met Trp Phe Phe Lys Gln Lys Glu Lys
            20   25   30

Glu Asp Gln Val Leu Ser Tyr Ile Asn Gly Val Thr Thr Ser Lys Pro
        35   40   45

Gly Val Ser Leu Val Tyr Ser Met Pro Ser Arg Asn Leu Ser Leu Arg
    50   55   60

Val Glu Gly Leu Gln Glu Lys Asp Ser Gly Pro Tyr Ser Cys Ser Val
65   70   75   80

<210> 36
<211> 60
<212> PRT
<213> Mus musculus

<400> 36
Gly Ala Asn Val Thr Leu Ser Cys Gln Ser Pro Arg Ser Lys Pro Ala
1   5   10   15

Val Gln Tyr Gln Trp Asp Arg Gln Leu Pro Ser Phe Gln Thr Phe Phe
            20   25   30

Ala Pro Ala Leu Asp Val Ile Arg Gly Ser Leu Ser Leu Thr Asn Leu
        35   40   45

Ser Ser Ser Met Ala Gly Val Tyr Val Cys Lys Ala
    50   55   60

<210> 37
<211> 1846
<212> DNA
<213> Mus musculus

<400> 37
gtcgacccac gcgtccggtg cacattcggg ttgccgccgc tcacccacaa cacctgtaga 60
caccgtgtgt ccaactctcc ctgagtactc cgggccaagg agggccatga ttcttcaggc 120
tggaaccccc gagaccagct tgctgcgggt tttgttcctg ggactgagta cccttgctgc 180
cttctcccga gctcagatgg agttgcacgt gcccccgggc ctcaacaaat tggaagcggt 240
agagggagaa gaagtggtgc tccccgcctg gtacacgatg gcacgggagg agtcgtggtc 300
ccaccccccgg gaggtgccca tcctgatctg gttcttggaa caagaaggga aggaaccaaa 360
ccaggtgttg tcttacatta atggagtcat gacaaataaa cctggaacag ccctggtcca 420
ctctatctct tcacggaatg tgtccctgcg cctgggggca ctccaggagg gagactctgg 480
gacttaccgc tgttctgtca atgtgcagaa tgatgaaggc aaaagtatag gccacagcat 540
caaaagcata gagctcaaag tgctggttcc tccagctcct ccatcctgta gtttacaggg 600
tgtaccctat gtcgggacca atgtgaccct gaactgcaag tccccaagga gtaaacctac 660
tgctcagtac cagtgggaga ggctggcccc atcctcccag gtcttctttg gaccagcctt 720
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<210> 38
<211> 1182
<212> DNA
<213> Mus musculus

<400> 38

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gaggagtcgt ggtcccaccc ccgggaggtg cccatcctga tctggttctt ggaacaagaa 240
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```

<210> 39
<211> 394
<212> PRT
<213> Mus musculus

<400> 39

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Met Ile Leu Gln Ala Gly Thr Pro Glu Thr Ser Leu Leu Arg Val Leu
1               5                   10                  15

Phe Leu Gly Leu Ser Thr Leu Ala Ala Phe Ser Arg Ala Gln Met Glu
            20                  25                  30

Leu His Val Pro Pro Gly Leu Asn Lys Leu Glu Ala Val Glu Gly Glu
        35                  40                  45

Glu Val Val Leu Pro Ala Trp Tyr Thr Met Ala Arg Glu Glu Ser Trp
    50                  55                  60

Ser His Pro Arg Glu Val Pro Ile Leu Ile Trp Phe Leu Glu Gln Glu
65                  70                  75                  80

Gly Lys Glu Pro Asn Gln Val Leu Ser Tyr Ile Asn Gly Val Met Thr
                85                  90                  95

Asn Lys Pro Gly Thr Ala Leu Val His Ser Ile Ser Ser Arg Asn Val
            100                 105                 110

Ser Leu Arg Leu Gly Ala Leu Gln Glu Gly Asp Ser Gly Thr Tyr Arg
        115                 120                 125

Cys Ser Val Asn Val Gln Asn Asp Glu Gly Lys Ser Ile Gly His Ser
    130                 135                 140

Ile Lys Ser Ile Glu Leu Lys Val Leu Val Pro Pro Ala Pro Pro Ser
145                 150                 155                 160

Cys Ser Leu Gln Gly Val Pro Tyr Val Gly Thr Asn Val Thr Leu Asn
```

                165   170   175

Cys Lys Ser Pro Arg Ser Lys Pro Thr Ala Gln Tyr Gln Trp Glu Arg
            180   185   190

Leu Ala Pro Ser Ser Gln Val Phe Phe Gly Pro Ala Leu Asp Ala Val
        195   200   205

Arg Gly Ser Leu Lys Leu Thr Asn Leu Ser Ile Ala Met Ser Gly Val
    210   215   220

Tyr Val Cys Lys Ala Gln Asn Arg Val Gly Phe Ala Lys Cys Asn Val
225   230   235   240

Thr Leu Asp Val Met Thr Gly Ser Lys Ala Ala Val Val Ala Gly Ala
                245   250   255

Val Val Gly Thr Phe Val Gly Leu Val Leu Ile Ala Gly Leu Val Leu
            260   265   270

Leu Tyr Gln Arg Arg Ser Lys Thr Leu Glu Glu Leu Ala Asn Asp Ile
        275   280   285

Lys Glu Asp Ala Ile Ala Pro Arg Thr Leu Pro Trp Thr Lys Gly Ser
    290   295   300

Asp Thr Ile Ser Lys Asn Gly Thr Leu Ser Ser Val Thr Ser Ala Arg
305   310   315   320

Ala Leu Arg Pro Pro Lys Ala Ala Pro Pro Arg Pro Gly Thr Phe Thr
                325   330   335

Pro Thr Pro Ser Val Ser Ser Gln Ala Leu Ser Ser Pro Arg Leu Pro
            340   345   350

Arg Val Asp Glu Pro Pro Pro Gln Ala Val Ser Leu Thr Pro Gly Gly
        355   360   365

Val Ser Ser Ser Ala Leu Ser Arg Met Gly Ala Val Pro Val Met Val
    370   375   380

Pro Ala Gln Ser Gln Ala Gly Ser Leu Val
385   390

<210> 40
<211> 365
<212> PRT
<213> Mus musculus

<400> 40
Gln Met Glu Leu His Val Pro Pro Gly Leu Asn Lys Leu Glu Ala Val
1   5   10   15

Glu Gly Glu Glu Val Val Leu Pro Ala Trp Tyr Thr Met Ala Arg Glu
            20   25   30

Glu Ser Trp Ser His Pro Arg Glu Val Pro Ile Leu Ile Trp Phe Leu

35 40 45

Glu Gln Glu Gly Lys Glu Pro Asn Gln Val Leu Ser Tyr Ile Asn Gly
50 55 60

Val Met Thr Asn Lys Pro Gly Thr Ala Leu Val His Ser Ile Ser Ser
65 70 75 80

Arg Asn Val Ser Leu Arg Leu Gly Ala Leu Gln Glu Gly Asp Ser Gly
85 90 95

Thr Tyr Arg Cys Ser Val Asn Val Gln Asn Asp Glu Gly Lys Ser Ile
100 105 110

Gly His Ser Ile Lys Ser Ile Glu Leu Lys Val Leu Val Pro Pro Ala
115 120 125

Pro Pro Ser Cys Ser Leu Gln Gly Val Pro Tyr Val Gly Thr Asn Val
130 135 140

Thr Leu Asn Cys Lys Ser Pro Arg Ser Lys Pro Thr Ala Gln Tyr Gln
145 150 155 160

Trp Glu Arg Leu Ala Pro Ser Ser Gln Val Phe Phe Gly Pro Ala Leu
165 170 175

Asp Ala Val Arg Gly Ser Leu Lys Leu Thr Asn Leu Ser Ile Ala Met
180 185 190

Ser Gly Val Tyr Val Cys Lys Ala Gln Asn Arg Val Gly Phe Ala Lys
195 200 205

Cys Asn Val Thr Leu Asp Val Met Thr Gly Ser Lys Ala Ala Val Val
210 215 220

Ala Gly Ala Val Val Gly Thr Phe Val Gly Leu Val Leu Ile Ala Gly
225 230 235 240

Leu Val Leu Leu Tyr Gln Arg Arg Ser Lys Thr Leu Glu Glu Leu Ala
245 250 255

Asn Asp Ile Lys Glu Asp Ala Ile Ala Pro Arg Thr Leu Pro Trp Thr
260 265 270

Lys Gly Ser Asp Thr Ile Ser Lys Asn Gly Thr Leu Ser Ser Val Thr
275 280 285

Ser Ala Arg Ala Leu Arg Pro Pro Lys Ala Ala Pro Pro Arg Pro Gly
290 295 300

Thr Phe Thr Pro Thr Pro Ser Val Ser Ser Gln Ala Leu Ser Ser Pro
305 310 315 320

Arg Leu Pro Arg Val Asp Glu Pro Pro Pro Gln Ala Val Ser Leu Thr
325 330 335

Pro Gly Gly Val Ser Ser Ser Ala Leu Ser Arg Met Gly Ala Val Pro
340 345 350

Val Met Val Pro Ala Gln Ser Gln Ala Gly Ser Leu Val
355 360 365

<210> 41
<211> 29
<212> PRT
<213> Mus musculus

<400> 41
Met Ile Leu Gln Ala Gly Thr Pro Glu Thr Ser Leu Leu Arg Val Leu
1 5 10 15

Phe Leu Gly Leu Ser Thr Leu Ala Ala Phe Ser Arg Ala
20 25

<210> 42
<211> 249
<212> PRT
<213> Mus musculus

<400> 42
Met Ile Leu Gln Ala Gly Thr Pro Glu Thr Ser Leu Leu Arg Val Leu
1 5 10 15

Phe Leu Gly Leu Ser Thr Leu Ala Ala Phe Ser Arg Ala Gln Met Glu
20 25 30

Leu His Val Pro Pro Gly Leu Asn Lys Leu Glu Ala Val Glu Gly Glu
35 40 45

Glu Val Val Leu Pro Ala Trp Tyr Thr Met Ala Arg Glu Glu Ser Trp
50 55 60

Ser His Pro Arg Glu Val Pro Ile Leu Ile Trp Phe Leu Glu Gln Glu
65 70 75 80

Gly Lys Glu Pro Asn Gln Val Leu Ser Tyr Ile Asn Gly Val Met Thr
85 90 95

Asn Lys Pro Gly Thr Ala Leu Val His Ser Ile Ser Ser Arg Asn Val
100 105 110

Ser Leu Arg Leu Gly Ala Leu Gln Glu Gly Asp Ser Gly Thr Tyr Arg
115 120 125

Cys Ser Val Asn Val Gln Asn Asp Glu Gly Lys Ser Ile Gly His Ser
130 135 140

Ile Lys Ser Ile Glu Leu Lys Val Leu Val Pro Pro Ala Pro Pro Ser
145 150 155 160

Cys Ser Leu Gln Gly Val Pro Tyr Val Gly Thr Asn Val Thr Leu Asn
165 170 175

Cys Lys Ser Pro Arg Ser Lys Pro Thr Ala Gln Tyr Gln Trp Glu Arg
180 185 190

```
Leu Ala Pro Ser Ser Gln Val Phe Phe Gly Pro Ala Leu Asp Ala Val
        195                 200                 205

Arg Gly Ser Leu Lys Leu Thr Asn Leu Ser Ile Ala Met Ser Gly Val
    210                 215                 220

Tyr Val Cys Lys Ala Gln Asn Arg Val Gly Phe Ala Lys Cys Asn Val
225                 230                 235                 240

Thr Leu Asp Val Met Thr Gly Ser Lys
                245


<210> 43
<211> 355
<212> PRT
<213> Mus musculus

<220>
<221> SITE
<222> (355)
<223> Xaa=unknown amino acid
<400> 43

Met Gly Pro Ser Thr Pro Leu Leu Ile Leu Phe Leu Leu Ser Trp Ser
  1               5                  10                  15

Gly Pro Leu Gln Gly Gln Gln His His Leu Val Glu Tyr Met Glu Arg
             20                  25                  30

Arg Leu Ala Ala Leu Glu Glu Arg Leu Ala Gln Cys Gln Asp Gln Ser
         35                  40                  45

Ser Arg His Ala Ala Glu Leu Arg Asp Phe Lys Asn Lys Met Leu Pro
     50                  55                  60

Leu Leu Glu Val Ala Glu Lys Glu Arg Glu Ala Leu Arg Thr Glu Ala
 65                  70                  75                  80

Asp Thr Ile Ser Gly Arg Val Asp Arg Leu Glu Arg Glu Val Asp Tyr
                 85                  90                  95

Leu Glu Thr Gln Asn Pro Ala Leu Pro Cys Val Glu Phe Asp Glu Lys
            100                 105                 110

Val Thr Gly Gly Pro Gly Thr Lys Gly Lys Gly Arg Arg Asn Glu Lys
        115                 120                 125

Tyr Asp Met Val Thr Asp Cys Gly Tyr Thr Ile Ser Gln Val Arg Ser
    130                 135                 140

Met Lys Ile Leu Lys Arg Phe Gly Gly Pro Ala Gly Leu Trp Thr Lys
145                 150                 155                 160

Asp Pro Leu Gly Gln Thr Glu Lys Ile Tyr Val Leu Asp Gly Thr Gln
                165                 170                 175

Asn Asp Thr Ala Phe Val Phe Pro Arg Leu Arg Asp Phe Thr Leu Ala
```

```
            180                     185                     190

Met Ala Ala Arg Lys Ala Ser Arg Val Arg Val Pro Phe Pro Trp Val
        195                     200                     205

Gly Thr Gly Gln Leu Val Tyr Gly Gly Phe Leu Tyr Phe Ala Arg Arg
    210                     215                     220

Pro Pro Gly Arg Pro Gly Gly Gly Gly Glu Met Glu Asn Thr Leu Gln
225                     230                     235                     240

Leu Ile Lys Phe His Leu Ala Asn Arg Thr Val Val Asp Ser Ser Val
                245                     250                     255

Phe Pro Ala Glu Gly Leu Ile Pro Pro Tyr Gly Leu Thr Ala Asp Thr
            260                     265                     270

Tyr Ile Asp Leu Ala Ala Asp Glu Glu Gly Leu Trp Ala Val Tyr Ala
        275                     280                     285

Thr Arg Glu Asp Asp Arg His Leu Cys Leu Ala Lys Leu Asp Pro Gln
    290                     295                     300

Thr Leu Asp Thr Glu Gln Gln Trp Asp Thr Pro Cys Pro Arg Glu Asn
305                     310                     315                     320

Ala Glu Ala Ala Phe Val Ile Cys Gly Thr Leu Tyr Val Val Tyr Asn
                325                     330                     335

Thr Arg Pro Ala Ser Arg Ala Arg Ile Gln Cys Ser Phe Asp Ala Ser
            340                     345                     350

Gly Pro Xaa
        355


<210> 44
<211> 25
<212> PRT
<213> Mus musculus

<400> 44
Ala Ala Val Val Ala Gly Ala Val Val Gly Thr Phe Val Gly Leu Val
  1               5                  10                  15

Leu Ile Ala Gly Leu Val Leu Leu Tyr
            20                  25


<210> 45
<211> 120
<212> PRT
<213> Mus musculus

<400> 45
Gln Arg Arg Ser Lys Thr Leu Glu Glu Leu Ala Asn Asp Ile Lys Glu
  1               5                  10                  15
```

```
Asp Ala Ile Ala Pro Arg Thr Leu Pro Trp Thr Lys Gly Ser Asp Thr
            20                  25                  30

Ile Ser Lys Asn Gly Thr Leu Ser Ser Val Thr Ser Ala Arg Ala Leu
        35                  40                  45

Arg Pro Pro Lys Ala Ala Pro Pro Arg Pro Gly Thr Phe Thr Pro Thr
    50                  55                  60

Pro Ser Val Ser Ser Gln Ala Leu Ser Ser Pro Arg Leu Pro Arg Val
65                  70                  75                  80

Asp Glu Pro Pro Pro Gln Ala Val Ser Leu Thr Pro Gly Gly Val Ser
                85                  90                  95

Ser Ser Ala Leu Ser Arg Met Gly Ala Val Pro Val Met Val Pro Ala
            100                 105                 110

Gln Ser Gln Ala Gly Ser Leu Val
        115                 120


<210> 46
<211> 1801
<212> DNA
<213> Homo sapiens

<400> 46
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tggttcctgt ttcactggct gttttagttt tgtgttaatt ggtgtttctg agcattcaaa 1740
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a 1801

<210> 47
<211> 735
<212> DNA
<213> Homo sapiens

<400> 47
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tgcaggccct tcggtgaaga caattcgatc ccagagtcct gtcctgactt ctgttgtggc 180
tcctgttcca gccaatactg ctgctctgac gtgctgaaga aaatccagtg gaatgaggaa 240
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accacaacta ctaccgtggt tcacaccgct taccctcagc ctcaacctgt ggcccccagc 540
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gcaccctacc caacgcagta ccctccaccc tacctggccc agcccacagg gccaccagcc 660
tatcatgaga cgttggctgg agccagccag cctccataca acccggccta catggatccc 720
ccaaaggcag ttccc 735

<210> 48
<211> 245
<212> PRT
<213> Homo sapiens

<400> 48
Met Arg Leu Phe Val Arg Pro Ser Val Arg Pro Ala Met Ala Ala Pro
1 5 10 15

Ala Pro Ser Pro Trp Thr Leu Ser Leu Leu Leu Leu Leu Leu Leu Pro
20 25 30

Ser Pro Gly Ala His Gly Glu Leu Cys Arg Pro Phe Gly Glu Asp Asn
35 40 45

Ser Ile Pro Glu Ser Cys Pro Asp Phe Cys Cys Gly Ser Cys Ser Ser
50 55 60

Gln Tyr Cys Cys Ser Asp Val Leu Lys Lys Ile Gln Trp Asn Glu Glu
65 70 75 80

Met Cys Pro Glu Pro Glu Ser Ser Arg Phe Ser Ala His Pro Glu Thr
85 90 95

Pro Glu Gln Leu Gly Ser Ala Leu Lys Tyr Gln Ser Ser Leu Asp Ser
100 105 110

Asp Asn Met Pro Gly Phe Gly Ala Thr Val Ala Ile Gly Leu Thr Val
115 120 125

Phe Val Val Phe Ile Ala Thr Ile Ile Val Cys Phe Thr Cys Ser Cys
130 135 140

Cys Cys Leu Tyr Lys Met Cys Cys Arg Pro Arg Pro Val Val Ser Asn
145 150 155 160

```
Thr Thr Thr Thr Thr Val Val His Thr Ala Tyr Pro Gln Pro Gln Pro
                165                 170                 175

Val Ala Pro Ser Tyr Pro Gly Pro Thr Tyr Gln Gly Tyr His Pro Met
            180                 185                 190

Pro Pro Gln Pro Gly Met Pro Ala Ala Pro Tyr Pro Thr Gln Tyr Pro
        195                 200                 205

Pro Pro Tyr Leu Ala Gln Pro Thr Gly Pro Pro Ala Tyr His Glu Thr
    210                 215                 220

Leu Ala Gly Ala Ser Gln Pro Pro Tyr Asn Pro Ala Tyr Met Asp Pro
225                 230                 235                 240

Pro Lys Ala Val Pro
                245


<210> 49
<211> 38
<212> PRT
<213> Homo sapiens

<400> 49
Met Arg Leu Phe Val Arg Pro Ser Val Arg Pro Ala Met Ala Ala Pro
  1               5                  10                  15

Ala Pro Ser Pro Trp Thr Leu Ser Leu Leu Leu Leu Leu Leu Leu Pro
            20                  25                  30

Ser Pro Gly Ala His Gly
        35


<210> 50
<211> 207
<212> PRT
<213> Homo sapiens

<400> 50
Glu Leu Cys Arg Pro Phe Gly Glu Asp Asn Ser Ile Pro Glu Ser Cys
  1               5                  10                  15

Pro Asp Phe Cys Cys Gly Ser Cys Ser Ser Gln Tyr Cys Cys Ser Asp
            20                  25                  30

Val Leu Lys Lys Ile Gln Trp Asn Glu Glu Met Cys Pro Glu Pro Glu
        35                  40                  45

Ser Ser Arg Phe Ser Ala His Pro Glu Thr Pro Glu Gln Leu Gly Ser
    50                  55                  60

Ala Leu Lys Tyr Gln Ser Ser Leu Asp Ser Asp Asn Met Pro Gly Phe
65                  70                  75                  80

Gly Ala Thr Val Ala Ile Gly Leu Thr Val Phe Val Val Phe Ile Ala
                85                  90                  95
```

Thr Ile Ile Val Cys Phe Thr Cys Ser Cys Cys Cys Leu Tyr Lys Met
100 105 110

Cys Cys Arg Pro Arg Pro Val Val Ser Asn Thr Thr Thr Thr Thr Val
115 120 125

Val His Thr Ala Tyr Pro Gln Pro Gln Pro Val Ala Pro Ser Tyr Pro
130 135 140

Gly Pro Thr Tyr Gln Gly Tyr His Pro Met Pro Pro Gln Pro Gly Met
145 150 155 160

Pro Ala Ala Pro Tyr Pro Thr Gln Tyr Pro Pro Pro Tyr Leu Ala Gln
165 170 175

Pro Thr Gly Pro Pro Ala Tyr His Glu Thr Leu Ala Gly Ala Ser Gln
180 185 190

Pro Pro Tyr Asn Pro Ala Tyr Met Asp Pro Pro Lys Ala Val Pro
195 200 205

<210> 51
<211> 85
<212> PRT
<213> Homo sapiens

<400> 51
Glu Leu Cys Arg Pro Phe Gly Glu Asp Asn Ser Ile Pro Glu Ser Cys
1 5 10 15

Pro Asp Phe Cys Cys Gly Ser Cys Ser Ser Gln Tyr Cys Cys Ser Asp
20 25 30

Val Leu Lys Lys Ile Gln Trp Asn Glu Glu Met Cys Pro Glu Pro Glu
35 40 45

Ser Ser Arg Phe Ser Ala His Pro Glu Thr Pro Glu Gln Leu Gly Ser
50 55 60

Ala Leu Lys Tyr Gln Ser Ser Leu Asp Ser Asp Asn Met Pro Gly Phe
65 70 75 80

Gly Ala Thr Val Ala
85

<210> 52
<211> 25
<212> PRT
<213> Homo sapiens

<400> 52
Ile Gly Leu Thr Val Phe Val Val Phe Ile Ala Thr Ile Ile Val Cys
1 5 10 15

Phe Thr Cys Ser Cys Cys Cys Leu Tyr
20 25

<210> 53
<211> 97
<212> PRT
<213> Homo sapiens

<400> 53
Lys Met Cys Cys Arg Pro Arg Pro Val Val Ser Asn Thr Thr Thr Thr
1 5 10 15

Thr Val Val His Thr Ala Tyr Pro Gln Pro Gln Pro Val Ala Pro Ser
20 25 30

Tyr Pro Gly Pro Thr Tyr Gln Gly Tyr His Pro Met Pro Pro Gln Pro
35 40 45

Gly Met Pro Ala Ala Pro Tyr Pro Thr Gln Tyr Pro Pro Pro Tyr Leu
50 55 60

Ala Gln Pro Thr Gly Pro Pro Ala Tyr His Glu Thr Leu Ala Gly Ala
65 70 75 80

Ser Gln Pro Pro Tyr Asn Pro Ala Tyr Met Asp Pro Pro Lys Ala Val
85 90 95

Pro

<210> 54
<211> 50
<212> PRT
<213> Homo sapiens

<400> 54
Cys Arg Pro Phe Gly Glu Asp Asn Ser Ile Pro Glu Ser Cys Pro Asp
1 5 10 15

Phe Cys Cys Gly Ser Cys Ser Ser Gln Tyr Cys Cys Ser Asp Val Leu
20 25 30

Lys Lys Ile Gln Trp Asn Glu Glu Met Cys Pro Glu Pro Glu Ser Ser
35 40 45

Arg Phe
50

<210> 55
<211> 56
<212> PRT
<213> Homo sapiens

<400> 55
Thr Val Phe Val Val Phe Ile Ala Thr Ile Ile Val Cys Phe Thr Cys
1 5 10 15

Ser Cys Cys Cys Leu Tyr Lys Met Cys Cys Arg Pro Arg Pro Val Val

20 25 30

Ser Asn Thr Thr Thr Thr Thr Val Val His Thr Ala Tyr Pro Gln Pro
35 40 45

Gln Pro Val Ala Pro Ser Tyr Pro
50 55

<210> 56
<211> 1858
<212> DNA
<213> Mus musculus

<400> 56
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tattgctgct gctgttgctg ctgccgccgc ctccgggtgc ccatggtgag ctgtgcaggc 180
cctttggtga agacaattcg atcccagtgt tctgtcctga tttctgttgt ggttcctgtt 240
ccaaccaata ctgctgctcg gacgtgctga ggaaaatcca gtggaatgag gaaatgtgtc 300
ctgagccaga gtccagcaga ttttccaccc ccgcggagga gacacccgaa catctgggtt 360
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tcgccattgg cgtgaccatc tttgtggtgt ttattgccac tatcatcatc tgcttcacct 480
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<210> 57
<211> 639
<212> DNA
<213> Mus musculus

<400> 57
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<210> 58
<211> 213
<212> PRT
<213> Mus musculus

<400> 58

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Leu Leu Pro Pro Pro Pro Gly Ala His Gly Glu Leu Cys Arg Pro Phe
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Gly Glu Asp Asn Ser Ile Pro Val Phe Cys Pro Asp Phe Cys Cys Gly
        35                  40                  45

Ser Cys Ser Asn Gln Tyr Cys Cys Ser Asp Val Leu Arg Lys Ile Gln
    50                  55                  60

Trp Asn Glu Glu Met Cys Pro Glu Pro Glu Ser Ser Arg Phe Ser Thr
65                  70                  75                  80

Pro Ala Glu Glu Thr Pro Glu His Leu Gly Ser Ala Leu Lys Phe Arg
                85                  90                  95

Ser Ser Phe Asp Ser Asp Pro Met Ser Gly Phe Gly Ala Thr Val Ala
            100                 105                 110

Ile Gly Val Thr Ile Phe Val Val Phe Ile Ala Thr Ile Ile Ile Cys
        115                 120                 125

Phe Thr Cys Ser Cys Cys Cys Leu Tyr Lys Met Cys Cys Pro Gln Arg
    130                 135                 140

Pro Val Val Thr Asn Thr Thr Thr Thr Thr Val Val His Ala Pro Tyr
145                 150                 155                 160

Pro Gln Pro Gln Pro Gln Pro Val Ala Pro Ser Tyr Pro Gly Pro Thr
                165                 170                 175

Tyr Gln Gly Tyr His Pro Met Pro Pro Pro Ala Arg Asn Ala Ser Ser
            180                 185                 190

Thr Leu Pro Asn Ala Val Pro Thr Thr Leu Pro Gly Pro Ala His Arg
        195                 200                 205

Ala Ala Thr Leu Pro
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<210> 59
<211> 26

<212> PRT
<213> Mus musculus

<400> 59
Met Ala Ala Pro Ala Pro Ser Leu Trp Thr Leu Leu Leu Leu Leu Leu
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Leu Leu Pro Pro Pro Pro Gly Ala His Gly
20 25

<210> 60
<211> 187
<212> PRT
<213> Mus musculus

<400> 60
Glu Leu Cys Arg Pro Phe Gly Glu Asp Asn Ser Ile Pro Val Phe Cys
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Pro Asp Phe Cys Cys Gly Ser Cys Ser Asn Gln Tyr Cys Cys Ser Asp
20 25 30

Val Leu Arg Lys Ile Gln Trp Asn Glu Glu Met Cys Pro Glu Pro Glu
35 40 45

Ser Ser Arg Phe Ser Thr Pro Ala Glu Glu Thr Pro Glu His Leu Gly
50 55 60

Ser Ala Leu Lys Phe Arg Ser Ser Phe Asp Ser Asp Pro Met Ser Gly
65 70 75 80

Phe Gly Ala Thr Val Ala Ile Gly Val Thr Ile Phe Val Val Phe Ile
85 90 95

Ala Thr Ile Ile Ile Cys Phe Thr Cys Ser Cys Cys Cys Leu Tyr Lys
100 105 110

Met Cys Cys Pro Gln Arg Pro Val Val Thr Asn Thr Thr Thr Thr Thr
115 120 125

Val Val His Ala Pro Tyr Pro Gln Pro Gln Pro Gln Pro Val Ala Pro
130 135 140

Ser Tyr Pro Gly Pro Thr Tyr Gln Gly Tyr His Pro Met Pro Pro Pro
145 150 155 160

Ala Arg Asn Ala Ser Ser Thr Leu Pro Asn Ala Val Pro Thr Thr Leu
165 170 175

Pro Gly Pro Ala His Arg Ala Ala Thr Leu Pro
180 185

<210> 61
<211> 86
<212> PRT
<213> Mus musculus

<400> 61
Glu Leu Cys Arg Pro Phe Gly Glu Asp Asn Ser Ile Pro Val Phe Cys
1 5 10 15

Pro Asp Phe Cys Cys Gly Ser Cys Ser Asn Gln Tyr Cys Cys Ser Asp
20 25 30

Val Leu Arg Lys Ile Gln Trp Asn Glu Glu Met Cys Pro Glu Pro Glu
35 40 45

Ser Ser Arg Phe Ser Thr Pro Ala Glu Glu Thr Pro Glu His Leu Gly
50 55 60

Ser Ala Leu Lys Phe Arg Ser Ser Phe Asp Ser Asp Pro Met Ser Gly
65 70 75 80

Phe Gly Ala Thr Val Ala
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<210> 62
<211> 25
<212> PRT
<213> Mus musculus

<400> 62
Ile Gly Val Thr Ile Phe Val Val Phe Ile Ala Thr Ile Ile Ile Cys
1 5 10 15

Phe Thr Cys Ser Cys Cys Cys Leu Tyr
20 25

<210> 63
<211> 76
<212> PRT
<213> Mus musculus

<400> 63
Lys Met Cys Cys Pro Gln Arg Pro Val Val Thr Asn Thr Thr Thr Thr
1 5 10 15

Thr Val Val His Ala Pro Tyr Pro Gln Pro Gln Pro Gln Pro Val Ala
20 25 30

Pro Ser Tyr Pro Gly Pro Thr Tyr Gln Gly Tyr His Pro Met Pro Pro
35 40 45

Pro Ala Arg Asn Ala Ser Ser Thr Leu Pro Asn Ala Val Pro Thr Thr
50 55 60

Leu Pro Gly Pro Ala His Arg Ala Ala Thr Leu Pro
65 70 75

<210> 64
<211> 50
<212> PRT

<213> Mus musculus

<400> 64
Cys Pro Asp Phe Cys Cys Gly Ser Cys Ser Asn Gln Tyr Cys Cys Ser
1 5 10 15

Asp Val Leu Arg Lys Ile Gln Trp Asn Glu Glu Met Cys Pro Glu Pro
20 25 30

Glu Ser Ser Arg Phe Ser Thr Pro Ala Glu Glu Thr Pro Glu His Leu
35 40 45

Gly Ser
50

<210> 65
<211> 56
<212> PRT
<213> Mus musculus

<400> 65
Cys Phe Thr Cys Ser Cys Cys Cys Leu Tyr Lys Met Cys Cys Pro Gln
1 5 10 15

Arg Pro Val Val Thr Asn Thr Thr Thr Thr Thr Val Val His Ala Pro
20 25 30

Tyr Pro Gln Pro Gln Pro Gln Pro Val Ala Pro Ser Tyr Pro Gly Pro
35 40 45

Thr Tyr Gln Gly Tyr His Pro Met
50 55

<210> 66
<211> 1927
<212> DNA
<213> Homo sapiens

<220>
<221> modified_base
<222> all "n" positions
<223> n=a, c, g, or t

<400> 66
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actctggcac cactctccag gctgccatgg ggcccagcac ccctctcctc atcttgttcc 120
ttttgtcatg gtcgggaccc ctccaaggac agcagcacca ccttgtggag tacatggaac 180
gccgactagc tgctttagag gaacggctgg cccagtgcca ggaccagagt agtcggcatg 240
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gagcgggagg cactcagaac tgaggccgac accatctccg ggagagtgga tcgtctggag 360
cgggaggtag actatctgga gacccagaac ccagctctgc cctgtgtaga gtttgatgag 420
aaggttgact ggaggccctg ggaccaaagg caagggaaga aggaatgaga agtacgatat 480
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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1860
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cgcagcc 1927

<210> 67
<211> 319
<212> PRT
<213> Homo sapiens

<400> 67
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Val Thr Val Asp Ala Ile Ser Val Glu Thr Pro Gln Asp Val Leu Arg
20 25 30

Ala Ser Gln Gly Lys Ser Val Thr Leu Pro Cys Thr Tyr His Thr Ser
35 40 45

Thr Ser Ser Arg Glu Gly Leu Ile Gln Trp Asp Lys Leu Leu Leu Thr
50 55 60

His Thr Glu Arg Val Val Ile Trp Pro Phe Ser Asn Lys Asn Tyr Ile
65 70 75 80

His Gly Glu Leu Tyr Lys Asn Arg Val Ser Ile Ser Asn Asn Ala Glu
85 90 95

Gln Ser Asp Ala Ser Ile Thr Ile Asp Gln Leu Thr Met Ala Asp Asn
100 105 110

Gly Thr Tyr Glu Cys Ser Val Ser Leu Met Ser Asp Leu Glu Gly Asn
115 120 125

Thr Lys Ser Arg Val Arg Leu Leu Val Leu Val Pro Pro Ser Lys Pro
130 135 140

Glu Cys Gly Ile Glu Gly Glu Thr Ile Ile Gly Asn Asn Ile Gln Leu
145 150 155 160

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Thr Cys Gln Ser Lys Glu Gly Ser Pro Thr Pro Gln Tyr Ser Trp Lys
                165                 170                 175

Arg Tyr Asn Ile Leu Asn Gln Glu Gln Pro Leu Ala Gln Pro Ala Ser
            180                 185                 190

Gly Gln Pro Val Ser Leu Lys Asn Ile Ser Thr Asp Thr Ser Gly Tyr
        195                 200                 205

Tyr Ile Cys Thr Ser Ser Asn Glu Glu Gly Thr Gln Phe Cys Asn Ile
    210                 215                 220

Thr Val Ala Val Arg Ser Pro Ser Met Asn Val Ala Leu Tyr Val Gly
225                 230                 235                 240

Ile Ala Val Gly Val Val Ala Ala Leu Ile Ile Ile Gly Ile Ile Ile
                245                 250                 255

Tyr Cys Cys Cys Cys Arg Gly Lys Asp Asp Asn Thr Glu Asp Lys Glu
            260                 265                 270

Asp Ala Arg Pro Asn Arg Glu Ala Tyr Glu Glu Pro Pro Glu Gln Leu
        275                 280                 285

Arg Glu Leu Ser Arg Glu Arg Glu Glu Glu Asp Asp Tyr Arg Gln Glu
    290                 295                 300

Glu Gln Arg Ser Thr Gly Arg Glu Ser Pro Asp His Leu Asp Gln
305                 310                 315


<210> 68
<211> 2793
<212> DNA
<213> Homo sapiens

<400> 68
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<210> 69
<211> 52
<212> PRT
<213> Homo sapiens

<400> 69
Lys Thr Ala Leu Gly Glu Leu Leu Lys Pro Leu Asn Ser Glu Tyr Gly
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Lys Val Ala Pro Gly Trp Gly Thr Thr Pro Leu Met Gly Val Phe Met
20 25 30

Ala Leu Phe Ala Val Phe Leu Leu Ile Ile Leu Glu Ile Tyr Asn Ser
35 40 45

Ser Val Leu Leu
50

<210> 70
<211> 1832
<212> DNA
<213> Homo sapiens

<220>
<221> modified_base
<222> all "n" positions
<223> n=a, c, g, or t

<400> 70
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aaactgcagt ggcccacgat gggaagaggg gaaagcccag gggtacagga ggcctctggg 120
tgaaggcaga ggctaacatg gggttcggag cgaccttggc cgttggctga ccatctttgt 180
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<210> 71
<211> 51
<212> PRT
<213> Mus musculus

<400> 71
Ser Pro Arg Ser Lys Pro Thr Ala Gln Tyr Gln Trp Glu Arg Leu Ala
1 5 10 15

Pro Ser Ser Gln Val Phe Phe Gly Pro Ala Leu Asp Ala Val Arg Gly
20 25 30

Ser Leu Lys Leu Thr Asn Leu Ser Ile Ala Met Ser Gly Val Tyr Val
35 40 45

Cys Lys Ala
50

<210> 72
<211> 2557
<212> DNA
<213> Homo sapiens

<400> 72
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tgacttgtgg gcagtgcctt ctgctgagcg agtcatggcc cgaaggcaga actaactgtg 120

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cctgcagtct tcactctcag gatgcagccg aggtgggccc aaggggccac gatgtggctt 180
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accctgcagt gcttcgcgga tgtcagcacc acctctcacg tcaagcctca gcaccagatg 360
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tattttattc ctgaagtccg gatctatgac tcagggacat ataaatgtac tgtgattgtg 480
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atggtcaagc tgaaaagaga gaagaattct cgagaccaga attttgtgat actggaattc 720
cccgttgagg aacaggaccg cgttttatcc ttccgatgtc aagctaggat catttctggg 780
atccatatgc agacctcaga atctaccaag agtgaactgg tcaccgtgac ggaatccttc 840
tctacaccca agttccacat cagccccacc ggaatgatca tggaaggagc tcagctccac 900
attaagtgca ccattcaagt gactcacctg gcccaggagt ttccagaaat cataattcag 960
aaggacaagg cgattgtggc ccacaacaga catggcaaca aggctgtgta ctcagtcatg 1020
gccatggtgg agcacagtgg caactacacg tgcaaagtgg agtccagccg catatccaag 1080
gtcagcagca tcgtggtcaa cataacagaa ctattttcca agcccgaact ggaatcttcc 1140
ttcacacatc tggaccaagg tgaaagactg aacctgtcct gctccatccc aggagcacct 1200
ccagccaact tcaccatcca gaaggaagat acgattgtgt cacagactca agatttcacc 1260
aagatagcct caaagtcgga cagtgggacg tatatctgca ctgcaggtat tgacaaagtg 1320
gtcaagaaaa gcaacacagt ccagatagtc gtatgtgaaa tgctctccca gcccaggatt 1380
tcttatgatg cccagtttga ggtcataaaa ggacagacca tcgaagtccg ttgcgaatcg 1440
atcagtggaa ctttgcctat ttcttaccaa cttttaaaaa caagtaaagt tttggagaat 1500
agtaccaaga actcaaatga tcctgcggta ttcaaagaca accccactga agacgtcgaa 1560
taccagtgtg ttgcagataa ttgccattcc catgccaaaa tgttaagtga ggttctgagg 1620
gtgaaggtga tagccccggt ggatgaggtc cagatttcta tcctgtcaag taaggtggtg 1680
gagtctggag aggacattgt gctgcaatgt gctgtgaatg aaggatctgg tcccatcacc 1740
tataagtttt acagagaaaa agagggcaaa cccttctatc aaatgacctc aaatgccacc 1800
caggcatttt ggaccaagca gaaggctagc aaggaacagg agggagagta ttactgcaca 1860
gccttcaaca gagccaacca cgcctccagt gtccccagaa gcaaaatact gacagtcaga 1920
gtcattcttg ccccatggaa gaaaggactt attgcagtgg ttatcatcgg agtgatcatt 1980
gctctcttga tcattgcggc caaatgttat tttctgagga aagccaaggc caagcagatg 2040
ccagtggaaa tgtccaggcc agcagtacca cttctgaact ccaacaacga gaaaatgtca 2100
gatcccaata tggaagctaa cagtcattac ggtcacaatg acgatgtcag aaaccatgca 2160
atgaaaccaa taaatgataa taaagagcct ctgaactcag acgtgcagta cacggaagtt 2220
caagtgtcct cagctgagtc tcacaaagat ctaggaaaga aggacacaga gacagtgtac 2280
agtgaagtcc ggaaagctgt ccctgatgcc gtggaaagca gatactctag aacggaaggc 2340
tcccttgatg gaacttagac agcaaggcca gatgcacatc cctggaagga catccatgtt 2400
ccgagaagaa cagataatcc ctgtatttca agacctctgt gcacttattt atgaacctgc 2460
cctgctccca cagaacacag caattcctca ggctaagctg ccggttctta aatccatcct 2520
gctaagttaa tgttgggtag aaagagatac agagggg                          2557
```

<210> 73
<211> 738
<212> PRT
<213> Homo sapiens

<400> 73

```
Met Gln Pro Arg Trp Ala Gln Gly Ala Thr Met Trp Leu Gly Val Leu
1               5                   10                  15

Leu Thr Leu Leu Leu Cys Ser Ser Leu Glu Gly Gln Glu Asn Ser Phe
            20                  25                  30

Thr Ile Asn Ser Val Asp Met Lys Ser Leu Pro Asp Trp Thr Val Gln
        35                  40                  45

Asn Gly Lys Asn Leu Thr Leu Gln Cys Phe Ala Asp Val Ser Thr Thr
```

50 55 60

Ser His Val Lys Pro Gln His Gln Met Leu Phe Tyr Lys Asp Asp Val
65 70 75 80

Leu Phe Tyr Asn Ile Ser Ser Met Lys Ser Thr Glu Ser Tyr Phe Ile
85 90 95

Pro Glu Val Arg Ile Tyr Asp Ser Gly Thr Tyr Lys Cys Thr Val Ile
100 105 110

Val Asn Asn Lys Glu Lys Thr Thr Ala Glu Tyr Gln Leu Leu Val Glu
115 120 125

Gly Val Pro Ser Pro Arg Val Thr Leu Asp Lys Lys Glu Ala Ile Gln
130 135 140

Gly Gly Ile Val Arg Val Asn Cys Ser Val Pro Glu Glu Lys Ala Pro
145 150 155 160

Ile His Phe Thr Ile Glu Lys Leu Glu Leu Asn Glu Lys Met Val Lys
165 170 175

Leu Lys Arg Glu Lys Asn Ser Arg Asp Gln Asn Phe Val Ile Leu Glu
180 185 190

Phe Pro Val Glu Glu Gln Asp Arg Val Leu Ser Phe Arg Cys Gln Ala
195 200 205

Arg Ile Ile Ser Gly Ile His Met Gln Thr Ser Glu Ser Thr Lys Ser
210 215 220

Glu Leu Val Thr Val Thr Glu Ser Phe Ser Thr Pro Lys Phe His Ile
225 230 235 240

Ser Pro Thr Gly Met Ile Met Glu Gly Ala Gln Leu His Ile Lys Cys
245 250 255

Thr Ile Gln Val Thr His Leu Ala Gln Glu Phe Pro Glu Ile Ile Ile
260 265 270

Gln Lys Asp Lys Ala Ile Val Ala His Asn Arg His Gly Asn Lys Ala
275 280 285

Val Tyr Ser Val Met Ala Met Val Glu His Ser Gly Asn Tyr Thr Cys
290 295 300

Lys Val Glu Ser Ser Arg Ile Ser Lys Val Ser Ser Ile Val Val Asn
305 310 315 320

Ile Thr Glu Leu Phe Ser Lys Pro Glu Leu Glu Ser Ser Phe Thr His
325 330 335

Leu Asp Gln Gly Glu Arg Leu Asn Leu Ser Cys Ser Ile Pro Gly Ala
340 345 350

Pro Pro Ala Asn Phe Thr Ile Gln Lys Glu Asp Thr Ile Val Ser Gln
355 360 365

Thr Gln Asp Phe Thr Lys Ile Ala Ser Lys Ser Asp Ser Gly Thr Tyr
370 375 380

Ile Cys Thr Ala Gly Ile Asp Lys Val Val Lys Lys Ser Asn Thr Val
385 390 395 400

Gln Ile Val Val Cys Glu Met Leu Ser Gln Pro Arg Ile Ser Tyr Asp
405 410 415

Ala Gln Phe Glu Val Ile Lys Gly Gln Thr Ile Glu Val Arg Cys Glu
420 425 430

Ser Ile Ser Gly Thr Leu Pro Ile Ser Tyr Gln Leu Leu Lys Thr Ser
435 440 445

Lys Val Leu Glu Asn Ser Thr Lys Asn Ser Asn Asp Pro Ala Val Phe
450 455 460

Lys Asp Asn Pro Thr Glu Asp Val Glu Tyr Gln Cys Val Ala Asp Asn
465 470 475 480

Cys His Ser His Ala Lys Met Leu Ser Glu Val Leu Arg Val Lys Val
485 490 495

Ile Ala Pro Val Asp Glu Val Gln Ile Ser Ile Leu Ser Ser Lys Val
500 505 510

Val Glu Ser Gly Glu Asp Ile Val Leu Gln Cys Ala Val Asn Glu Gly
515 520 525

Ser Gly Pro Ile Thr Tyr Lys Phe Tyr Arg Glu Lys Glu Gly Lys Pro
530 535 540

Phe Tyr Gln Met Thr Ser Asn Ala Thr Gln Ala Phe Trp Thr Lys Gln
545 550 555 560

Lys Ala Ser Lys Glu Gln Glu Gly Glu Tyr Tyr Cys Thr Ala Phe Asn
565 570 575

Arg Ala Asn His Ala Ser Ser Val Pro Arg Ser Lys Ile Leu Thr Val
580 585 590

Arg Val Ile Leu Ala Pro Trp Lys Lys Gly Leu Ile Ala Val Val Ile
595 600 605

Ile Gly Val Ile Ile Ala Leu Leu Ile Ile Ala Ala Lys Cys Tyr Phe
610 615 620

Leu Arg Lys Ala Lys Ala Lys Gln Met Pro Val Glu Met Ser Arg Pro
625 630 635 640

Ala Val Pro Leu Leu Asn Ser Asn Asn Glu Lys Met Ser Asp Pro Asn
645 650 655

Met Glu Ala Asn Ser His Tyr Gly His Asn Asp Asp Val Arg Asn His
660 665 670

Ala Met Lys Pro Ile Asn Asp Asn Lys Glu Pro Leu Asn Ser Asp Val

```
        675                 680                 685

Gln Tyr Thr Glu Val Gln Val Ser Ser Ala Glu Ser His Lys Asp Leu
    690                 695                 700

Gly Lys Lys Asp Thr Glu Thr Val Tyr Ser Glu Val Arg Lys Ala Val
705                 710                 715                 720

Pro Asp Ala Val Glu Ser Arg Tyr Ser Arg Thr Glu Gly Ser Leu Asp
                725                 730                 735

Gly Thr
```

<210> 74
<211> 601
<212> DNA
<213> Rattus norvegicus

<220>
<221> modified_base
<222> all "n" positions
<223> n=a, c, g, or t

<400> 74

```
gnnnnnnagg tntanagncn cctttacncc gccgcggacg cgtgggcgga cgcgtggggt 60
gctgtggagc aagaagcaac ccgaagctag gagtctgtca gcgagggcag gggctgcctg 120
gttggggtag gagtgggagc agggccagca ggagggtctg aggaagccat tcaaagcgag 180
cagctgggag agctggggag ccgggaaggg cctacagact acaagagagg atcctggcgt 240
ctgggcctcc tgggtcatca ccatgaggcc acttcttgcc ctgctgcttc tgggtctggc 300
atcaggctct cctcctctgg acgacaacaa gatccccagc ctgtgtcccg ggcagcccgg 360
cctcccaggc acaccaggcc accacggcag ccaaggcctg cctggccgtg acggccgtga 420
tggccgcgac ggtgcacccg gagctccggg agagaaaggc gagggcggga gaccgggact 480
acctgggcca cgtngggagc ccgggccgcg tggagaggca ggacctgtgg gggctatcgg 540
gcctggnggg gaatgctcgg tgccccacga tcagcttcag tgccaagcga tcagaaagcc 600
c                                                                 601
```

<210> 75
<211> 732
<212> DNA
<213> Rattus norvegicus

<220>
<221> modified_base
<222> all "n" positions
<223> n=a, c, g, or t

<400> 75

```
gngngttnnn ttccncctcc gacttaaggc tgccatgggg cccagtgctc ctctgctcct 60
cttcttcctt ttgtcatggc cgggacccct tcagggacag cagcaccacc ttgtggagta 120
catggaacgc cgactagctg ccttagagga gcggctggca cagtgccagg atcagagcag 180
tcggcatgct gctgagcttc gggacttcaa aaacaagatg ctgcctctac tggaggtggc 240
agagaaggag cgggaaacac tcagaaccga ggcagacagc atttcaggaa gagtggaccg 300
tcttgaacgg gaagtagact acctggagac acagaaccca gctttgccct gtgtagaact 360
ggatgagaag gtgactggag gccctggaac caaaggcaag ggccggagaa atgagaaata 420
cgatatggtg acagactgta gctacacaat ctctcaggtg aggtcaatga agatcctgaa 480
gcggtttggt ggctcagctg gcctatggac caaggatcca ctggggccag canagaagat 540
```

```
ctacgtgtta gacggnacgc agaacgacac ggccttcgtt ttccganggt gcgtgactta 600
ccctcaccat ggctgccgca aagttccgaa tcgggtgccc ttncctgggt agnacaagaa 660
aactggtgtn tgtggcttcc tttttatctc aangcntctg gaggaacttg nangggggn 720
nggtggnaaa at                                                     732
```

```
<210> 76
<211> 177
<212> PRT
<213> Homo sapiens

<400> 76
Gln Leu Gln Leu His Leu Pro Ala Asn Arg Leu Gln Ala Val Glu Glu
1               5                   10                  15
Gly Glu Ser Gly Ala Ser Ala Trp Tyr Thr Leu His Arg Glu Val Ser
            20                  25                  30
Ser Ser Gln Pro Trp Glu Val Pro Phe Val Met Trp Phe Phe Lys Gln
        35                  40                  45
Lys Glu Lys Glu Asp Gln Val Leu Ser Tyr Ile Asn Gly Val Thr Thr
    50                  55                  60
Ser Lys Pro Gly Val Ser Leu Val Tyr Ser Met Pro Ser Arg Asn Leu
65                  70                  75                  80
Ser Leu Arg Val Glu Gly Leu Gln Glu Lys Asp Ser Gly Pro Tyr Ser
                85                  90                  95
Cys Ser Val Asn Val Gln Asp Lys Gln Gly Lys Ser Arg Gly His Ser
            100                 105                 110
Ile Lys Thr Leu Glu Leu Asn Val Leu Val Pro Pro Ala Pro Pro Ser
        115                 120                 125
Cys Arg Leu Gln Gly Val Pro His Val Gly Ala Asn Val Thr Leu Ser
    130                 135                 140
Cys Gln Ser Pro Arg Ser Lys Pro Ala Val Gln Tyr Gln Trp Asp Arg
145                 150                 155                 160
Gln Leu Pro Ser Phe Gln Thr Phe Phe Ala Pro Ala Leu Asp Val Ile
                165                 170                 175
Arg
```

```
<210> 77
<211> 735
<212> DNA
<213> Homo sapiens

<400> 77
atgcgtctgt ttgtccgtcc gtccgtccgt cccgccatgg ctgcgccggc gccctctccg     60
tggacccttt cgctgctgct gttgttgcta ctgccgtctc cgggtgccca tggcgagctg    120
tgcaggccct tcggtgaaga caattcgatc ccagagtcct gtcctgactt ctgttgtggc    180
tcctgttcca gccaatactg ctgctctgac gtgctgaaga aaatccagtg gaatgaggaa    240
atgtgccctg agccagagtc cagcagattt tccgcccacc cggagacacc agaacagctg    300
ggttcagcgc tgaagtatca gtccagtctt gacagtgaca acatgccagg gttcggagcg    360
accgtggcca tcggcctgac cgtcttcgtg gtgtttatcg ctaccatcat tgtgtgcttt    420
acctgctcct gctgctgtct atataagatg tgctgccgcc cacgacctgt cgtgtccaac    480
accacaacta ctaccgtggt tcacaccgct taccctcagc ctcaacctgt ggcccccagc    540
tatcctggac caacatacca gggctaccat cccatgcccc cccagccagg aatgccagca    600
gcaccctacc caacgcagta ccctccaccc tacctggccc agcccacagg gccaccagcc    660
tatcatgaga cgttggctgg agccagccag cctccataca acccggccta catggatccc    720
ccaaaggtag ttccc                                                     735

<210> 78
```

<211> 18
<212> PRT
<213> Homo sapiens

<400> 78
Gly Ser Leu Ser Leu Thr Asn Leu Ser Ser Ser Met Ala Gly Val Tyr
1 5 10 15
Val Cys

<210> 79
<211> 22
<212> PRT
<213> Homo sapiens

<400> 79
Lys Ala His Asn Glu Val Gly Thr Ala Gln Cys Asn Val Thr Leu Glu
1 5 10 15
Val Ser Thr Gly Pro Gly
20

<210> 80
<211> 728
<212> DNA
<213> Homo sapiens

<400> 80
atgaggccac tcctcgtcct gctgctcctg ggcctggcgg ccggctcgcc cccactggac 60
gacaacaaga tccccagcct ctgcccgggg caccccggcc ttccaggcac gccgggccac 120
catggcagcc agggcttgcc gggccgcgat ggccgcgacg gccgcgacgg cgcgcccggg 180
gctccgggag agaaaggcga gggcgggagg cgggactgcc gggacctcga ggggaccccg 240
ggccgcgagg agaggcggga cccgcggggc ccaccgggcc tgccggggag tgctcggtgc 300
ctccgcgatc cgccttcagc gccaagcgct ccgagagccg ggtgcctccg ccgtctgacg 360
caccccttgcc cttcgaccgc gtgctggtga acgagcaggg acattacgac gccgtcaccg 420
gcaagttcac ctgccaggtg cctggggtct actacttcgc cgtccatgcc accgtctacc 480
gggccagcct gcagtttgat ctggtgaaga atggcgaatc ccttgcctct ttcttccagt 540
ttttcggggg gtggcccaag ccagcctcgc tctcgggggg ggccatggtg aggctggagc 600
ctgaggacca agtgtgggtg caggtgggtg tgggtgacta cattggcatc tatgccagca 660
tcaagacaga cagcaccttc tccggatttc tggtgtactc cgactggcac agctccccag 720
tctttgct 728

<210> 81
<211> 206
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (13)
<223> Xaa=unknown amino acid

<400> 81
Met Ile Ser Leu Pro Gly Pro Leu Val Thr Asn Leu Xaa Arg Phe Leu
1 5 10 15
Phe Leu Gly Leu Ser Ala Leu Ala Pro Pro Ser Arg Ala Gln Leu Gln
20 25 30
Leu His Leu Pro Ala Asn Arg Leu Gln Ala Val Glu Glu Gly Glu Ser
35 40 45

```
Gly Ala Ser Ala Trp Tyr Thr Leu His Arg Glu Val Ser Ser Ser Gln
    50                  55                  60
Pro Trp Glu Val Pro Phe Val Met Trp Phe Phe Lys Gln Lys Glu Lys
65                  70                  75                  80
Glu Asp Gln Val Leu Ser Tyr Ile Asn Gly Val Thr Thr Ser Lys Pro
                85                  90                  95
Gly Val Ser Leu Val Tyr Ser Met Pro Ser Arg Asn Leu Ser Leu Arg
            100                 105                 110
Val Glu Gly Leu Gln Glu Lys Asp Ser Gly Pro Tyr Ser Cys Ser Val
        115                 120                 125
Asn Val Gln Asp Lys Gln Gly Lys Ser Arg Gly His Ser Ile Lys Thr
    130                 135                 140
Leu Glu Leu Asn Val Leu Val Pro Pro Ala Pro Pro Ser Cys Arg Leu
145                 150                 155                 160
Gln Gly Val Pro His Val Gly Ala Asn Val Thr Leu Ser Cys Gln Ser
                165                 170                 175
Pro Arg Ser Lys Pro Ala Val Gln Tyr Gln Trp Asp Arg Gln Leu Pro
            180                 185                 190
Ser Phe Gln Thr Phe Phe Ala Pro Ala Leu Asp Val Ile Arg
        195                 200                 205

<210> 82
<211> 217
<212> PRT
<213> Homo sapiens

<400> 82
Gln Leu Gln Leu His Leu Pro Ala Asn Arg Leu Gln Ala Val Glu Glu
 1               5                  10                  15
Gly Glu Ser Gly Ala Ser Ala Trp Tyr Thr Leu His Arg Glu Val Ser
            20                  25                  30
Ser Ser Gln Pro Trp Glu Val Pro Phe Val Met Trp Phe Phe Lys Gln
        35                  40                  45
Lys Glu Lys Glu Asp Gln Val Leu Ser Tyr Ile Asn Gly Val Thr Thr
    50                  55                  60
Ser Lys Pro Gly Val Ser Leu Val Tyr Ser Met Pro Ser Arg Asn Leu
65                  70                  75                  80
Ser Leu Arg Val Glu Gly Leu Gln Glu Lys Asp Ser Gly Pro Tyr Ser
                85                  90                  95
Cys Ser Val Asn Val Gln Asp Lys Gln Gly Lys Ser Arg Gly His Ser
            100                 105                 110
Ile Lys Thr Leu Glu Leu Asn Val Leu Val Pro Pro Ala Pro Pro Ser
        115                 120                 125
Cys Arg Leu Gln Gly Val Pro His Val Gly Ala Asn Val Thr Leu Ser
    130                 135                 140
Cys Gln Ser Pro Arg Ser Lys Pro Ala Val Gln Tyr Gln Trp Asp Arg
145                 150                 155                 160
Gln Leu Pro Ser Phe Gln Thr Phe Phe Ala Pro Ala Leu Asp Val Ile
                165                 170                 175
Arg Gly Ser Leu Ser Leu Thr Asn Leu Ser Ser Ser Met Ala Gly Val
            180                 185                 190
Tyr Val Cys Lys Ala His Asn Glu Val Gly Thr Ala Gln Cys Asn Val
        195                 200                 205
Thr Leu Glu Val Ser Thr Gly Pro Gly
    210                 215

<210> 83
<211> 220
```

<212> PRT
<213> Homo sapiens

<400> 83
Gln Leu Gln Leu His Leu Pro Ala Asn Arg Leu Gln Ala Val Glu Glu
1 5 10 15
Gly Glu Ser Gly Ala Ser Ala Trp Tyr Thr Leu His Arg Glu Val Ser
20 25 30
Ser Ser Gln Pro Trp Glu Val Pro Phe Val Met Trp Phe Phe Lys Gln
35 40 45
Lys Glu Lys Glu Asp Gln Val Leu Ser Tyr Ile Asn Gly Val Thr Thr
50 55 60
Ser Lys Pro Gly Val Ser Leu Val Tyr Ser Met Pro Ser Arg Asn Leu
65 70 75 80
Ser Leu Arg Val Glu Gly Leu Gln Glu Lys Asp Ser Gly Pro Tyr Ser
85 90 95
Cys Ser Val Asn Val Gln Asp Lys Gln Gly Lys Ser Arg Gly His Ser
100 105 110
Ile Lys Thr Leu Glu Leu Asn Val Leu Val Pro Pro Ala Pro Pro Ser
115 120 125
Cys Arg Leu Gln Gly Val Pro His Val Gly Ala Asn Val Thr Leu Ser
130 135 140
Cys Gln Ser Pro Arg Ser Lys Pro Ala Val Gln Tyr Gln Trp Asp Arg
145 150 155 160
Gln Leu Pro Ser Phe Gln Thr Phe Phe Ala Pro Ala Leu Asp Val Ile
165 170 175
Arg Gly Ser Leu Ser Leu Thr Asn Leu Ser Ser Ser Met Ala Gly Val
180 185 190
Tyr Val Cys Lys Ala His Asn Glu Val Gly Thr Ala Gln Cys Asn Val
195 200 205
Thr Leu Glu Val Ser Thr Gly Pro Gly Ala Ala Val
210 215 220

<210> 84
<211> 202
<212> PRT
<213> Homo sapiens

<400> 84
Met Gly Pro Ser Thr Pro Leu Leu Ile Leu Phe Leu Leu Ser Trp Ser
1 5 10 15
Gly Pro Leu Gln Gly Gln Gln His His Leu Val Glu Tyr Met Glu Arg
20 25 30
Arg Leu Ala Ala Leu Glu Glu Arg Leu Ala Gln Cys Gln Asp Gln Ser
35 40 45
Ser Arg His Ala Ala Glu Leu Arg Asp Phe Lys Asn Lys Met Leu Pro
50 55 60
Leu Leu Glu Val Ala Glu Lys Glu Arg Glu Ala Leu Arg Thr Glu Ala
65 70 75 80
Asp Thr Ile Ser Gly Arg Val Asp Arg Leu Glu Arg Glu Val Asp Tyr
85 90 95
Leu Glu Thr Gln Asn Pro Ala Leu Pro Cys Val Glu Phe Asp Glu Lys
100 105 110
Val Thr Gly Gly Pro Gly Thr Lys Gly Lys Gly Arg Arg Asn Glu Lys
115 120 125
Tyr Asp Met Val Thr Asp Cys Gly Tyr Thr Ile Ser Gln Val Arg Ser
130 135 140
Met Lys Ile Leu Lys Arg Phe Gly Gly Pro Ala Gly Leu Trp Thr Lys

```
145                 150                 155                 160
Asp Pro Leu Gly Gln Thr Glu Lys Ile Tyr Val Leu Asp Gly Thr Gln
                165                 170                 175
Asn Asp Thr Ala Phe Val Phe Pro Arg Leu Arg Asp Phe Thr Leu Ala
            180                 185                 190
Met Ala Ala Arg Lys Ala Ser Arg Val Arg
        195                 200
```

<210> 85
<211> 67
<212> PRT
<213> Homo sapiens

<400> 85

```
Ala Ser Arg Ala Arg Ile Gln Cys Ser Phe Asp Ala Ser Gly Thr Leu
 1               5                  10                  15
Thr Pro Glu Arg Ala Ala Leu Pro Tyr Phe Pro Arg Arg Tyr Gly Ala
            20                  25                  30
His Ala Ser Leu Arg Tyr Asn Pro Arg Glu Arg Gln Leu Tyr Ala Trp
        35                  40                  45
Asp Asp Gly Tyr Gln Ile Val Tyr Lys Leu Glu Met Arg Lys Lys Glu
    50                  55                  60
Glu Glu Val
65
```

<210> 86
<211> 19
<212> PRT
<213> Homo sapiens

<400> 86

```
Val Pro Phe Pro Trp Val Gly Thr Gly Gln Leu Val Tyr Gly Gly Phe
 1               5                  10                  15
Leu Tyr Phe
```

<210> 87
<211> 17
<212> PRT
<213> Homo sapiens

<400> 87

```
Ala Glu Ala Ala Phe Val Ile Cys Gly Thr Leu Tyr Val Val Tyr Asn
 1               5                  10                  15
Thr
```

<210> 88
<211> 99
<212> PRT
<213> Homo sapiens

<400> 88

```
Ala Arg Arg Pro Pro Gly Arg Pro Gly Gly Gly Gly Glu Met Glu Asn
 1               5                  10                  15
Thr Leu Gln Leu Ile Lys Phe His Leu Ala Asn Arg Thr Val Val Asp
            20                  25                  30
Ser Ser Val Phe Pro Ala Glu Gly Leu Ile Pro Pro Tyr Gly Leu Thr
```

```
        35                  40                  45
Ala Asp Thr Tyr Ile Asp Leu Ala Ala Asp Glu Glu Gly Leu Trp Ala
    50                  55                  60
Val Tyr Ala Thr Arg Glu Asp Asp Arg His Leu Cys Leu Ala Lys Leu
65                  70                  75                  80
Asp Pro Gln Thr Leu Asp Thr Glu Gln Gln Trp Asp Thr Pro Cys Pro
                85                  90                  95
Arg Glu Asn
```

<210> 89
<211> 320
<212> PRT
<213> Homo sapiens

<400> 89

```
Met Gly Pro Ser Thr Pro Leu Leu Ile Leu Phe Leu Leu Ser Trp Ser
1               5                   10                  15
Gly Pro Leu Gln Gly Gln Gln His His Leu Val Glu Tyr Met Glu Arg
            20                  25                  30
Arg Leu Ala Ala Leu Glu Glu Arg Leu Ala Gln Cys Gln Asp Gln Ser
        35                  40                  45
Ser Arg His Ala Ala Glu Leu Arg Asp Phe Lys Asn Lys Met Leu Pro
    50                  55                  60
Leu Leu Glu Val Ala Glu Lys Glu Arg Glu Ala Leu Arg Thr Glu Ala
65                  70                  75                  80
Asp Thr Ile Ser Gly Arg Val Asp Arg Leu Glu Arg Glu Val Asp Tyr
                85                  90                  95
Leu Glu Thr Gln Asn Pro Ala Leu Pro Cys Val Glu Phe Asp Glu Lys
            100                 105                 110
Val Thr Gly Gly Pro Gly Thr Lys Gly Lys Gly Arg Arg Asn Glu Lys
        115                 120                 125
Tyr Asp Met Val Thr Asp Cys Gly Tyr Thr Ile Ser Gln Val Arg Ser
    130                 135                 140
Met Lys Ile Leu Lys Arg Phe Gly Gly Pro Ala Gly Leu Trp Thr Lys
145                 150                 155                 160
Asp Pro Leu Gly Gln Thr Glu Lys Ile Tyr Val Leu Asp Gly Thr Gln
                165                 170                 175
Asn Asp Thr Ala Phe Val Phe Pro Arg Leu Arg Asp Phe Thr Leu Ala
            180                 185                 190
Met Ala Ala Arg Lys Ala Ser Arg Val Arg Val Pro Phe Pro Trp Val
        195                 200                 205
Gly Thr Gly Gln Leu Val Tyr Gly Gly Phe Leu Tyr Phe Ala Arg Arg
    210                 215                 220
Pro Pro Gly Arg Pro Gly Gly Gly Gly Glu Met Glu Asn Thr Leu Gln
225                 230                 235                 240
Leu Ile Lys Phe His Leu Ala Asn Arg Thr Val Val Asp Ser Ser Val
                245                 250                 255
Phe Pro Ala Glu Gly Leu Ile Pro Pro Tyr Gly Leu Thr Ala Asp Thr
            260                 265                 270
Tyr Ile Asp Leu Ala Ala Asp Glu Glu Gly Leu Trp Ala Val Tyr Ala
        275                 280                 285
Thr Arg Glu Asp Asp Arg His Leu Cys Leu Ala Lys Leu Asp Pro Gln
    290                 295                 300
Thr Leu Asp Thr Glu Gln Gln Trp Asp Thr Pro Cys Pro Arg Glu Asn
305                 310                 315                 320
```

<210> 90

<211> 385
<212> PRT
<213> Homo sapiens

<400> 90

```
Gln Gln His His Leu Val Glu Tyr Met Glu Arg Arg Leu Ala Ala Leu
1               5                   10                  15
Glu Glu Arg Leu Ala Gln Cys Gln Asp Gln Ser Ser Arg His Ala Ala
            20                  25                  30
Glu Leu Arg Asp Phe Lys Asn Lys Met Leu Pro Leu Leu Glu Val Ala
        35                  40                  45
Glu Lys Glu Arg Glu Ala Leu Arg Thr Glu Ala Asp Thr Ile Ser Gly
    50                  55                  60
Arg Val Asp Arg Leu Glu Arg Glu Val Asp Tyr Leu Glu Thr Gln Asn
65                  70                  75                  80
Pro Ala Leu Pro Cys Val Glu Phe Asp Glu Lys Val Thr Gly Gly Pro
                85                  90                  95
Gly Thr Lys Gly Lys Gly Arg Arg Asn Glu Lys Tyr Asp Met Val Thr
            100                 105                 110
Asp Cys Gly Tyr Thr Ile Ser Gln Val Arg Ser Met Lys Ile Leu Lys
        115                 120                 125
Arg Phe Gly Gly Pro Ala Gly Leu Trp Thr Lys Asp Pro Leu Gly Gln
    130                 135                 140
Thr Glu Lys Ile Tyr Val Leu Asp Gly Thr Gln Asn Asp Thr Ala Phe
145                 150                 155                 160
Val Phe Pro Arg Leu Arg Asp Phe Thr Leu Ala Met Ala Ala Arg Lys
                165                 170                 175
Ala Ser Arg Val Arg Val Pro Phe Pro Trp Val Gly Thr Gly Gln Leu
            180                 185                 190
Val Tyr Gly Gly Phe Leu Tyr Phe Ala Arg Arg Pro Pro Gly Arg Pro
        195                 200                 205
Gly Gly Gly Gly Glu Met Glu Asn Thr Leu Gln Leu Ile Lys Phe His
    210                 215                 220
Leu Ala Asn Arg Thr Val Val Asp Ser Ser Val Phe Pro Ala Glu Gly
225                 230                 235                 240
Leu Ile Pro Pro Tyr Gly Leu Thr Ala Asp Thr Tyr Ile Asp Leu Ala
                245                 250                 255
Ala Asp Glu Glu Gly Leu Trp Ala Val Tyr Ala Thr Arg Glu Asp Asp
            260                 265                 270
Arg His Leu Cys Leu Ala Lys Leu Asp Pro Gln Thr Leu Asp Thr Glu
        275                 280                 285
Gln Gln Trp Asp Thr Pro Cys Pro Arg Glu Asn Ala Glu Ala Ala Phe
    290                 295                 300
Val Ile Cys Gly Thr Leu Tyr Val Val Tyr Asn Thr Arg Pro Ala Ser
305                 310                 315                 320
Arg Ala Arg Ile Gln Cys Ser Phe Asp Ala Ser Gly Thr Leu Thr Pro
                325                 330                 335
Glu Arg Ala Ala Leu Pro Tyr Phe Pro Arg Arg Tyr Gly Ala His Ala
            340                 345                 350
Ser Leu Arg Tyr Asn Pro Arg Glu Arg Gln Leu Tyr Ala Trp Asp Asp
        355                 360                 365
Gly Tyr Gln Ile Val Tyr Lys Leu Glu Met Arg Lys Lys Glu Glu Glu
    370                 375                 380
Val
385
```

<210> 91
<211> 728

<212> DNA
<213> Homo sapiens

<400> 91
atgaggccac tcctcgtcct gctgctcctg ggcctggcgg ccggctcgcc cccactggac 60
gacaacaaga tccccagcct ctgcccgggg caccccggcc ttccaggcac gccgggccac 120
catggcagcc agggcttgcc gggccgcgat ggccgcgacg gccgcgacgg tgcgcccggg 180
gctccgggag agaaaggcga gggcgggagg cgggactgcc gggacctcga ggggaccccg 240
ggccgcgagg agaggcggga cccgcggggc ccaccgggcc tgccggggag tgctcggtgc 300
ctccgcgatc cgccttcagc gccaagcgct ccgagagccg ggtgcctccg ccgtctgacg 360
caccccttgcc cttcgaccgc gtgctggtga acgagcaggg acattacgac gccgtcaccg 420
gcaagttcac ctgccaggtg cctggggtct actacttcgc cgtccatgcc accgtctacc 480
gggccagcct gcagtttgat ctggtgaaga atggcgaatc cattgcctct ttcttccagt 540
tttcgggggg gtggcccaag ccagcctcgc tctcgggggg ggccatggtg aggctggagc 600
ctgaggacca agtgtgggtg caggtgggtg tgggtgacta cattggcatc tatgccagca 660
tcaagacaga cagcaccttc tccggatttc tggtgtactc cgactggcac agctccccag 720
tctttgct 728

<210> 92
<211> 69
<212> PRT
<213> Homo sapiens

<400> 92
Arg Pro Ala Ser Arg Ala Arg Ile Gln Cys Ser Phe Asp Ala Ser Gly
1 5 10 15
Thr Leu Thr Pro Glu Arg Ala Ala Leu Pro Tyr Phe Pro Arg Arg Tyr
20 25 30
Gly Ala His Ala Ser Leu Arg Tyr Asn Pro Arg Glu Arg Gln Leu Tyr
35 40 45
Ala Trp Asp Asp Gly Tyr Gln Ile Val Tyr Lys Leu Glu Met Arg Lys
50 55 60
Lys Glu Glu Glu Val
65

<210> 93
<211> 202
<212> PRT
<213> Mus musculus

<400> 93
Met Gly Pro Ser Ala Pro Leu Leu Leu Leu Phe Phe Leu Ser Trp Thr
1 5 10 15
Gly Pro Leu Gln Gly Gln Gln His His Leu Val Glu Tyr Met Glu Arg
20 25 30
Arg Leu Ala Ala Leu Glu Glu Arg Leu Ala Gln Cys Gln Asp Gln Ser
35 40 45
Ser Arg His Ala Ala Glu Leu Arg Asp Phe Lys Asn Lys Met Leu Pro
50 55 60
Leu Leu Glu Val Ala Glu Lys Glu Arg Glu Thr Leu Arg Thr Glu Ala
65 70 75 80
Asp Ser Ile Ser Gly Arg Val Asp Arg Leu Glu Arg Glu Val Asp Tyr
85 90 95
Leu Glu Thr Gln Asn Pro Ala Leu Pro Cys Val Glu Leu Asp Glu Lys
100 105 110
Val Thr Gly Gly Pro Gly Ala Lys Gly Lys Gly Arg Arg Asn Glu Lys
115 120 125
Tyr Asp Met Val Thr Asp Cys Ser Tyr Thr Val Ala Gln Val Arg Ser

```
    130                 135                 140
Met Lys Ile Leu Lys Arg Phe Gly Gly Ser Val Gly Leu Trp Thr Lys
145                 150                 155                 160
Asp Pro Leu Gly Pro Ala Glu Lys Ile Tyr Val Leu Asp Gly Thr Gln
                165                 170                 175
Asn Asp Thr Ala Phe Val Phe Pro Arg Leu Arg Asp Phe Thr Leu Ala
            180                 185                 190
Met Ala Ala Arg Lys Ala Ser Arg Ile Arg
        195                 200
```

<210> 94
<211> 69
<212> PRT
<213> Mus musculus

<400> 94

```
Arg Pro Ala Ser Arg Ala Arg Ile Gln Cys Ser Phe Asp Ala Ser Gly
1               5                   10                  15
Thr Leu Ala Pro Glu Arg Ala Ala Leu Ser Tyr Phe Pro Arg Arg Tyr
            20                  25                  30
Gly Ala His Ala Ser Leu Arg Tyr Asn Pro Arg Glu Arg Gln Leu Tyr
        35                  40                  45
Ala Trp Asp Asp Gly Tyr Gln Ile Val Tyr Lys Leu Glu Met Lys Lys
    50                  55                  60
Lys Glu Glu Glu Val
65
```

<210> 95
<211> 19
<212> PRT
<213> Mus musculus

<400> 95

```
Val Pro Phe Pro Trp Val Gly Thr Gly Gln Leu Val Tyr Gly Gly Phe
1               5                   10                  15
Leu Tyr Tyr
```

<210> 96
<211> 16
<212> PRT
<213> Mus musculus

<400> 96

```
Glu Ala Ala Phe Val Ile Cys Gly Thr Leu Tyr Val Val Tyr Asn Thr
1               5                   10                  15
```

<210> 97
<211> 99
<212> PRT
<213> Mus musculus

<400> 97

```
Ala Arg Arg Pro Pro Gly Gly Pro Gly Gly Gly Gly Glu Leu Glu Asn
1               5                   10                  15
Thr Leu Gln Leu Ile Lys Phe His Leu Ala Asn Arg Thr Val Val Asp
            20                  25                  30
Ser Ser Val Phe Pro Ala Glu Ser Leu Ile Pro Pro Tyr Gly Leu Thr
```

35 40 45
Ala Asp Thr Tyr Ile Asp Leu Ala Ala Asp Glu Glu Gly Leu Trp Ala
50 55 60
Val Tyr Ala Thr Arg Asp Asp Asp Arg His Leu Cys Leu Ala Lys Leu
65 70 75 80
Asp Pro Gln Thr Leu Asp Thr Glu Gln Gln Trp Asp Thr Pro Cys Pro
85 90 95
Arg Glu Asn

<210> 98
<211> 320
<212> PRT
<213> Mus musculus

<400> 98
Met Gly Pro Ser Ala Pro Leu Leu Leu Leu Phe Phe Leu Ser Trp Thr
1 5 10 15
Gly Pro Leu Gln Gly Gln Gln His His Leu Val Glu Tyr Met Glu Arg
20 25 30
Arg Leu Ala Ala Leu Glu Glu Arg Leu Ala Gln Cys Gln Asp Gln Ser
35 40 45
Ser Arg His Ala Ala Glu Leu Arg Asp Phe Lys Asn Lys Met Leu Pro
50 55 60
Leu Leu Glu Val Ala Glu Lys Glu Arg Glu Thr Leu Arg Thr Glu Ala
65 70 75 80
Asp Ser Ile Ser Gly Arg Val Asp Arg Leu Glu Arg Glu Val Asp Tyr
85 90 95
Leu Glu Thr Gln Asn Pro Ala Leu Pro Cys Val Glu Leu Asp Glu Lys
100 105 110
Val Thr Gly Gly Pro Gly Ala Lys Gly Lys Gly Arg Arg Asn Glu Lys
115 120 125
Tyr Asp Met Val Thr Asp Cys Ser Tyr Thr Val Ala Gln Val Arg Ser
130 135 140
Met Lys Ile Leu Lys Arg Phe Gly Gly Ser Val Gly Leu Trp Thr Lys
145 150 155 160
Asp Pro Leu Gly Pro Ala Glu Lys Ile Tyr Val Leu Asp Gly Thr Gln
165 170 175
Asn Asp Thr Ala Phe Val Phe Pro Arg Leu Arg Asp Phe Thr Leu Ala
180 185 190
Met Ala Ala Arg Lys Ala Ser Arg Ile Arg Val Pro Phe Pro Trp Val
195 200 205
Gly Thr Gly Gln Leu Val Tyr Gly Gly Phe Leu Tyr Tyr Ala Arg Arg
210 215 220
Pro Pro Gly Gly Pro Gly Gly Gly Gly Glu Leu Glu Asn Thr Leu Gln
225 230 235 240
Leu Ile Lys Phe His Leu Ala Asn Arg Thr Val Val Asp Ser Ser Val
245 250 255
Phe Pro Ala Glu Ser Leu Ile Pro Pro Tyr Gly Leu Thr Ala Asp Thr
260 265 270
Tyr Ile Asp Leu Ala Ala Asp Glu Glu Gly Leu Trp Ala Val Tyr Ala
275 280 285
Thr Arg Asp Asp Asp Arg His Leu Cys Leu Ala Lys Leu Asp Pro Gln
290 295 300
Thr Leu Asp Thr Glu Gln Gln Trp Asp Thr Pro Cys Pro Arg Glu Asn
305 310 315 320

<210> 99

<211> 299
<212> PRT
<213> Mus musculus

<400> 99
Gln Gln His His Leu Val Glu Tyr Met Glu Arg Arg Leu Ala Ala Leu
1 5 10 15
Glu Glu Arg Leu Ala Gln Cys Gln Asp Gln Ser Ser Arg His Ala Ala
20 25 30
Glu Leu Arg Asp Phe Lys Asn Lys Met Leu Pro Leu Leu Glu Val Ala
35 40 45
Glu Lys Glu Arg Glu Thr Leu Arg Thr Glu Ala Asp Ser Ile Ser Gly
50 55 60
Arg Val Asp Arg Leu Glu Arg Glu Val Asp Tyr Leu Glu Thr Gln Asn
65 70 75 80
Pro Ala Leu Pro Cys Val Glu Leu Asp Glu Lys Val Thr Gly Gly Pro
85 90 95
Gly Ala Lys Gly Lys Gly Arg Arg Asn Glu Lys Tyr Asp Met Val Thr
100 105 110
Asp Cys Ser Tyr Thr Val Ala Gln Val Arg Ser Met Lys Ile Leu Lys
115 120 125
Arg Phe Gly Gly Ser Val Gly Leu Trp Thr Lys Asp Pro Leu Gly Pro
130 135 140
Ala Glu Lys Ile Tyr Val Leu Asp Gly Thr Gln Asn Asp Thr Ala Phe
145 150 155 160
Val Phe Pro Arg Leu Arg Asp Phe Thr Leu Ala Met Ala Ala Arg Lys
165 170 175
Ala Ser Arg Ile Arg Val Pro Phe Pro Trp Val Gly Thr Gly Gln Leu
180 185 190
Val Tyr Gly Gly Phe Leu Tyr Tyr Ala Arg Arg Pro Pro Gly Gly Pro
195 200 205
Gly Gly Gly Gly Glu Leu Glu Asn Thr Leu Gln Leu Ile Lys Phe His
210 215 220
Leu Ala Asn Arg Thr Val Val Asp Ser Ser Val Phe Pro Ala Glu Ser
225 230 235 240
Leu Ile Pro Pro Tyr Gly Leu Thr Ala Asp Thr Tyr Ile Asp Leu Ala
245 250 255
Ala Asp Glu Glu Gly Leu Trp Ala Val Tyr Ala Thr Arg Asp Asp Asp
260 265 270
Arg His Leu Cys Leu Ala Lys Leu Asp Pro Gln Thr Leu Asp Thr Glu
275 280 285
Gln Gln Trp Asp Thr Pro Cys Pro Arg Glu Asn
290 295

<210> 100
<211> 728
<212> DNA
<213> Homo sapiens

<400> 100
atgaggccac tcctcgtcct gctgctcctg ggcctggcgg ccggctcgcc cccactggac 60
gacaacaaga tccccagcct ctgcccgggg caccccggcc ttccaggcac gccgggccac 120
catggcagcc agggcttgcc gggccgcgat ggccgcgacg gccgcgacgg cgcgcccggg 180
gctccgggag agaaaggcga gggcgggagg cgggactgcc gggacctcga ggggaccccg 240
ggccgcgagg agaggcggga cccgcggggc ccaccgggcc tgtcggggag tgctcggtgc 300
ctccgcgatc cgccttcagc gccaagcgct ccgagagccg ggtgcctccg ccgtctgacg 360
caccccttgcc cttcgaccgc gtgctggtga acgagcaggg acattacgac gccgtcaccg 420
gcaagttcac ctgccaggtg cctggggtct actacttcgc cgtccatgcc accgtctacc 480

```
gggccagcct gcagtttgat ctggtgaaga atggcgaatc cattgcctct ttcttccagt     540
ttttcggggg gtggcccaag ccagcctcgc tctcgggggg ggccatggtg aggctggagc     600
ctgaggacca agtgtgggtg caggtgggtg tgggtgacta cattggcatc tatgccagca     660
tcaagacaga cagcaccttc tccggatttc tggtgtactc cgactggcac agctccccag     720
tctttgct                                                              728
```

<210> 101
<211> 728
<212> DNA
<213> Homo sapiens

<400> 101

```
atgaggccac tcctcgtcct gctgctcctg ggcctggcgg ccggctcgcc cccactggac      60
gacaacaaga tccccagcct ctgcccgggg caccccggcc ttccaggcac gccgggccac     120
catggcagcc agggcttgcc gggccgcgat ggccgcgacg gccgcgacgg cgcgcccggg     180
gctccgggag agaaaggcga gggcgggagg cgggactgcc gggacctcga ggggaccccg     240
ggccgcgagg agaggcggga cccgcggggc ccaccgggcc tgccggggag tgctcggtgc     300
ctccgcgatc cgccttcagc gccaagcgct ccgagagccg ggtgcctccg ccgtctgacg     360
caccccttgcc cttcgaccgc gtgctggtga acgagcaggg acattacgac gccgtcaccg    420
gcaagttcac ctgccaggtg cctggggtct actacttcgc cgtccatgcc accgtctacc     480
gggccagcct gcagtttgat ctggtgaaga atggcgaatc cattgcctct ttcttccagt     540
ttttcggggg gtggcccaag ccagcctcgc tctcgggggg ggccatggtg aggctggagc     600
ctgaggacca agtgtgggtg caggtgggtg tgggtgacta cattggcatc tatgccagca     660
tcaagacaga cagcaccttc tccggatttc tggtgtactc cgactggcac agctccccag     720
tctttgct                                                              728
```

<210> 102
<211> 243
<212> PRT
<213> Homo sapiens

<400> 102

```
Met Arg Pro Leu Leu Val Leu Leu Leu Leu Gly Leu Ala Ala Gly Ser
 1               5                  10                  15
Pro Pro Leu Asp Asp Asn Lys Ile Pro Ser Leu Cys Pro Gly His Pro
            20                  25                  30
Gly Leu Pro Gly Thr Pro Gly His His Gly Ser Gln Gly Leu Pro Gly
        35                  40                  45
Arg Asp Gly Arg Asp Gly Arg Asp Gly Val Pro Gly Ala Pro Gly Glu
    50                  55                  60
Lys Gly Glu Gly Gly Arg Pro Gly Leu Pro Gly Pro Arg Gly Asp Pro
65                  70                  75                  80
Gly Pro Arg Gly Glu Ala Gly Pro Ala Gly Pro Thr Gly Pro Ala Gly
                85                  90                  95
Glu Cys Ser Val Pro Pro Arg Ser Ala Phe Ser Ala Lys Arg Ser Glu
            100                 105                 110
Ser Arg Val Pro Pro Pro Ser Asp Ala Pro Leu Pro Phe Asp Arg Val
        115                 120                 125
Leu Val Asn Glu Gln Gly His Tyr Asp Ala Val Thr Gly Lys Phe Thr
    130                 135                 140
Cys Gln Val Pro Gly Val Tyr Tyr Phe Ala Val His Ala Thr Val Tyr
145                 150                 155                 160
Arg Ala Ser Leu Gln Phe Asp Leu Val Lys Asn Gly Glu Ser Ile Ala
                165                 170                 175
Ser Phe Phe Gln Phe Phe Gly Gly Trp Pro Lys Pro Ala Ser Leu Ser
            180                 185                 190
Gly Gly Ala Met Val Arg Leu Glu Pro Glu Asp Gln Val Trp Val Gln
        195                 200                 205
```

Val Gly Val Gly Asp Tyr Ile Gly Ile Tyr Ala Ser Ile Lys Thr Asp
210 215 220
Ser Thr Phe Ser Gly Phe Leu Val Tyr Ser Asp Trp His Ser Ser Pro
225 230 235 240
Val Phe Ala

<210> 103
<211> 1338
<212> DNA
<213> Homo sapiens

<400> 103
gtcgacccac gcgtccggga ctggggtgac ggcagggcag ggggcgcctg gccggggaga 60
agcgcggggg ctggagcacc accaactgga gggtccggag tagcgagcgc cccgaaggag 120
gccatcgggg agccgggagg ggggactgcg agaggacccc ggcgtccggg ctcccggtgc 180
cagcgctatg aggccactcc tcgtcctgct gctcctgggc ctggcggccg gctcgccccc 240
actggacgac aacaagatcc ccagcctctg cccggggcac cccggccttc caggcacgcc 300
gggccaccat ggcagccagg gcttgccggg ccgcgatggc cgcgacggcc gcgacggtgc 360
gcccggggct ccgggagaga aaggcgaggg cgggaggcgg gactgccggg acctcgaggg 420
gaccccgggc cgcgaggaga ggcgggaccc gcggggccca ccgggcctgc cggggagtgc 480
tcggtgcctc cgcgatccgc cttcagcgcc aagcgctccg agagccgggt gcctccgccg 540
tctgacgcac ccttgccctt cgaccgcgtg ctggtgaacg agcagggaca ttacgacgcc 600
gtcaccggca agttcacctg ccaggtgcct ggggtctact acttcgccgt ccatgccacc 660
gtctaccggg ccagcctgca gtttgatctg gtgaagaatg gcgaatccat tgcctctttc 720
ttccagtttt tcgggggggtg gcccaagcca gcctcgctct cgggggggc catggtgagg 780
ctggagcctg aggaccaagt gtgggtgcag gtgggtgtgg gtgactacat tggcatctat 840
gccagcatca agacagacag caccttctcc ggatttctgg tgtactccga ctggcacagc 900
tccccagtct ttgcttagtg cccactgcaa agtgagctca tgctctcact cctagaagga 960
gggtgtgagg ctgacaacct ggtcatccag gagggctggc ccccctggaa tattgtgaat 1020
gactagggag gtggggtaga gcactctccg tcctgctgct ggcaaggaat gggaacagtg 1080
gctgtctgcg atcaggtctg gcagcatggg gcagtggctg gatttctgcc caagaccaga 1140
ggagtgtgct gtgctggcaa gtgtaagtcc cccagttgct ctggtccagg agcccacggt 1200
ggggtgctct cttcctggtc ctctgcttct ctggatcctc cccacccccct cctgctcctg 1260
gggccggccc ttttctcaga gatcactcaa taaacctaag aaccctccaa aaaaaaaaa 1320
aaaaaaaagg gcggccgc 1338

<210> 104
<211> 243
<212> PRT
<213> Homo sapiens

<400> 104
Met Arg Pro Leu Leu Val Leu Leu Leu Leu Gly Leu Ala Ala Gly Ser
1 5 10 15
Pro Pro Leu Asp Asp Asn Lys Ile Pro Ser Leu Cys Pro Gly His Pro
20 25 30
Gly Leu Pro Gly Thr Pro Gly His His Gly Ser Gln Gly Leu Pro Gly
35 40 45
Arg Asp Gly Arg Asp Gly Arg Asp Gly Ala Pro Gly Ala Pro Gly Glu
50 55 60
Lys Gly Glu Gly Gly Arg Pro Gly Leu Pro Gly Pro Arg Gly Asp Pro
65 70 75 80
Gly Pro Arg Gly Glu Ala Gly Pro Ala Gly Pro Thr Gly Pro Val Gly
85 90 95
Glu Cys Ser Val Pro Pro Arg Ser Ala Phe Ser Ala Lys Arg Ser Glu
100 105 110
Ser Arg Val Pro Pro Pro Ser Asp Ala Pro Leu Pro Phe Asp Arg Val

```
        115                     120                     125
Leu Val Asn Glu Gln Gly His Tyr Asp Ala Val Thr Gly Lys Phe Thr
    130                     135                     140
Cys Gln Val Pro Gly Val Tyr Tyr Phe Ala Val His Ala Thr Val Tyr
145                     150                     155                     160
Arg Ala Ser Leu Gln Phe Asp Leu Val Lys Asn Gly Glu Ser Ile Ala
                165                     170                     175
Ser Phe Phe Gln Phe Phe Gly Gly Trp Pro Lys Pro Ala Ser Leu Ser
            180                     185                     190
Gly Gly Ala Met Val Arg Leu Glu Pro Glu Asp Gln Val Trp Val Gln
        195                     200                     205
Val Gly Val Gly Asp Tyr Ile Gly Ile Tyr Ala Ser Ile Lys Thr Asp
    210                     215                     220
Ser Thr Phe Ser Gly Phe Leu Val Tyr Ser Asp Trp His Ser Ser Pro
225                     230                     235                     240
Val Phe Ala
```

<210> 105
<211> 1338
<212> DNA
<213> Homo sapiens

<400> 105

```
gtcgacccac gcgtccggga ctggggtgac ggcagggcag gggcgcctg gccggggaga     60
agcgcggggg ctggagcacc accaactgga gggtccggag tagcgagcgc cccgaaggag    120
gccatcgggg agccgggagg ggggactgcg agaggacccc ggcgtccggg ctcccggtgc    180
cagcgctatg aggccactcc tcgtcctgct gctcctgggc ctggcggccg gctcgccccc    240
actggacgac aacaagatcc ccagcctctg cccggggcac cccggccttc caggcacgcc    300
gggccaccat ggcagccagg gcttgccggg ccgcgatggc cgcgacggcc gcgacggcgc    360
gcccggggct ccgggagaga aaggcgaggg cgggaggcgg gactgccggg acctcgaggg    420
gaccccgggc cgcgaggaga ggcgggaccc gcggggccca ccgggcctgt cggggagtgc    480
tcggtgcctc cgcgatccgc cttcagcgcc aagcgctccg agagccgggt gcctccgccg    540
tctgacgcac ccttgccctt cgaccgcgtg ctggtgaacg agcagggaca ttacgacgcc    600
gtcaccggca agttcacctg ccaggtgcct ggggtctact acttcgccgt ccatgccacc    660
gtctaccggg ccagcctgca gtttgatctg gtgaagaatg gcgaatccat tgcctctttc    720
ttccagtttt tcggggggtg gcccaagcca gcctcgctct cggggggggc catggtgagg    780
ctggagcctg aggaccaagt gtgggtgcag gtgggtgtgg gtgactacat tggcatctat    840
gccagcatca agacagacag caccttctcc ggatttctgg tgtactccga ctggcacagc    900
tccccagtct ttgcttagtg cccactgcaa agtgagctca tgctctcact cctagaagga    960
gggtgtgagg ctgacaacct ggtcatccag gagggctggc ccccctggaa tattgtgaat   1020
gactagggag gtggggtaga gcactctccg tcctgctgct ggcaaggaat gggaacagtg   1080
gctgtctgcg atcaggtctg gcagcatggg gcagtggctg gatttctgcc caagaccaga   1140
ggagtgtgct gtgctggcaa gtgtaagtcc cccagttgct ctggtccagg agcccacggt   1200
ggggtgctct cttcctggtc ctctgcttct ctggatcctc cccacccccct cctgctcctg   1260
gggccggccc ttttctcaga gatcactcaa taaacctaag aaccctccaa aaaaaaaaaa   1320
aaaaaaaagg gcggccgc                                                  1338
```

<210> 106
<211> 243
<212> PRT
<213> Homo sapiens

<400> 106

```
Met Arg Pro Leu Leu Val Leu Leu Leu Leu Gly Leu Ala Ala Gly Ser
 1               5                  10                  15
Pro Pro Leu Asp Asp Asn Lys Ile Pro Ser Leu Cys Pro Gly His Pro
            20                  25                  30
```

```
Gly Leu Pro Gly Thr Pro Gly His His Gly Ser Gln Gly Leu Pro Gly
        35                  40                  45
Arg Asp Gly Arg Asp Gly Arg Asp Gly Ala Pro Gly Ala Pro Gly Glu
    50                  55                  60
Lys Gly Glu Gly Gly Arg Pro Gly Leu Pro Gly Pro Arg Gly Asp Pro
65                  70                  75                  80
Gly Pro Arg Gly Glu Ala Gly Pro Ala Gly Pro Thr Gly Pro Ala Gly
                85                  90                  95
Glu Cys Ser Val Pro Pro Arg Ser Ala Phe Ser Ala Lys Arg Ser Glu
            100                 105                 110
Ser Arg Val Pro Pro Pro Ser Asp Ala Pro Leu Pro Phe Asp Arg Val
        115                 120                 125
Leu Ala Asn Glu Gln Gly His Tyr Asp Ala Val Thr Gly Lys Phe Thr
    130                 135                 140
Cys Gln Val Pro Gly Val Tyr Tyr Phe Ala Val His Ala Thr Val Tyr
145                 150                 155                 160
Arg Ala Ser Leu Gln Phe Asp Leu Val Lys Asn Gly Glu Ser Ile Ala
                165                 170                 175
Ser Phe Phe Gln Phe Phe Gly Gly Trp Pro Lys Pro Ala Ser Leu Ser
            180                 185                 190
Gly Gly Ala Met Val Arg Leu Glu Pro Glu Asp Gln Val Trp Val Gln
        195                 200                 205
Val Gly Val Gly Asp Tyr Ile Gly Ile Tyr Ala Ser Ile Lys Thr Asp
    210                 215                 220
Ser Thr Phe Ser Gly Phe Leu Val Tyr Ser Asp Trp His Ser Ser Pro
225                 230                 235                 240
Val Phe Ala
```

<210> 107
<211> 1338
<212> DNA
<213> Homo sapiens

<400> 107

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gtcgacccac gcgtccggga ctggggtgac ggcagggcag gggcgcctg gccggggaga      60
agcgcggggg ctggagcacc accaactgga gggtccggag tagcgagcgc cccgaaggag    120
gccatcgggg agccgggagg ggggactgcg agaggacccc ggcgtccggg ctcccggtgc    180
cagcgctatg aggccactcc tcgtcctgct gctcctgggc ctggcggccg gctcgccccc    240
actggacgac aacaagatcc ccagcctctg cccggggcac ccccggccttc caggcacgcc    300
gggccaccat ggcagccagg gcttgccggg ccgcgatggc cgcgacggcc gcgacggcgc    360
gcccggggct ccgggagaga aaggcgaggg cgggaggcgg gactgccggg acctcgaggg    420
gaccccgggc cgcgaggaga ggcgggaccc gcggggccca ccgggcctgc cggggagtgc    480
tcggtgcctc cgcgatccgc cttcagcgcc aagcgctccg agagccgggt gcctccgccg    540
tctgacgcac ccttgccctt cgaccgcgtg ctggcgaacg agcagggaca ttacgacgcc    600
gtcaccggca agttcacctg ccaggtgcct ggggtctact acttcgccgt ccatgccacc    660
gtctaccggg ccagcctgca gtttgatctg gtgaagaatg gcgaatccat tgcctctttc    720
ttccagtttt tcgggggggtg gcccaagcca gcctcgctct cggggggggc catggtgagg    780
ctggagcctg aggaccaagt gtgggtgcag gtgggtgtgg gtgactacat tggcatctat    840
gccagcatca agacagacag caccttctcc ggatttctgg tgtactccga ctggcacagc    900
tccccagtct ttgcttagtg cccactgcaa agtgagctca tgctctcact cctagaagga    960
gggtgtgagg ctgacaacct ggtcatccag gagggctggc ccccctggaa tattgtgaat   1020
gactagggag gtggggtaga gcactctccg tcctgctgct ggcaaggaat gggaacagtg   1080
gctgtctgcg atcaggtctg gcagcatggg gcagtggctg gatttctgcc caagaccaga   1140
ggagtgtgct gtgctggcaa gtgtaagtcc cccagttgct ctggtccagg agcccacggt   1200
ggggtgctct cttcctggtc ctctgcttct ctggatcctc cccacccccct cctgctcctg   1260
gggccggccc ttttctcaga gatcactcaa taaacctaag aaccctccaa aaaaaaaaaa   1320
aaaaaaaagg gcggccgc                                                 1338
```

<210> 108
<211> 243
<212> PRT
<213> Homo sapiens

<400> 108
Met Arg Pro Leu Leu Val Leu Leu Leu Leu Gly Leu Ala Ala Gly Ser
1 5 10 15
Pro Pro Leu Asp Asp Asn Lys Ile Pro Ser Leu Cys Pro Gly His Pro
20 25 30
Gly Leu Pro Gly Thr Pro Gly His His Gly Ser Gln Gly Leu Pro Gly
35 40 45
Arg Asp Gly Arg Asp Gly Arg Asp Gly Ala Pro Gly Ala Pro Gly Glu
50 55 60
Lys Gly Glu Gly Gly Arg Pro Gly Leu Pro Gly Pro Arg Gly Asp Pro
65 70 75 80
Gly Pro Arg Gly Glu Ala Gly Pro Ala Gly Pro Thr Gly Pro Ala Gly
85 90 95
Glu Cys Ser Val Pro Pro Arg Ser Ala Phe Ser Ala Lys Arg Ser Glu
100 105 110
Ser Arg Val Pro Pro Pro Ser Asp Ala Pro Leu Pro Phe Asp Arg Val
115 120 125
Leu Val Asn Glu Gln Gly His Tyr Asp Ala Val Thr Gly Lys Phe Thr
130 135 140
Cys Gln Val Pro Gly Val Tyr Tyr Phe Ala Val His Ala Thr Val Tyr
145 150 155 160
Arg Ala Ser Leu Gln Phe Asp Leu Val Lys Asn Gly Glu Ser Leu Ala
165 170 175
Ser Phe Phe Gln Phe Phe Gly Gly Trp Pro Lys Pro Ala Ser Leu Ser
180 185 190
Gly Gly Ala Met Val Arg Leu Glu Pro Glu Asp Gln Val Trp Val Gln
195 200 205
Val Gly Val Gly Asp Tyr Ile Gly Ile Tyr Ala Ser Ile Lys Thr Asp
210 215 220
Ser Thr Phe Ser Gly Phe Leu Val Tyr Ser Asp Trp His Ser Ser Pro
225 230 235 240
Val Phe Ala

<210> 109
<211> 1338
<212> DNA
<213> Homo sapiens

<400> 109
gtcgacccac gcgtccggga ctggggtgac ggcagggcag gggcgcctg gccggggaga 60
agcgcggggg ctggagcacc accaactgga gggtccggag tagcgagcgc cccgaaggag 120
gccatcgggg agccgggagg ggggactgcg agaggacccc ggcgtccggg ctcccggtgc 180
cagcgctatg aggccactcc tcgtcctgct gctcctgggc ctggcggccg gctcgccccc 240
actggacgac aacaagatcc ccagcctctg cccggggcac cccggccttc caggcacgcc 300
gggccaccat ggcagccagg gcttgccggg ccgcgatggc cgcgacggcc gcgacggcgc 360
gcccggggct ccgggagaga aaggcgaggg cgggaggcgg gactgccggg acctcgaggg 420
gaccccgggc cgcgaggaga ggcgggaccc gcggggccca ccgggcctgc cggggagtgc 480
tcggtgcctc cgcgatccgc cttcagcgcc aagcgctccg agagccgggt gcctccgccg 540
tctgacgcac ccttgccctt cgaccgcgtg ctggtgaacg agcagggaca ttacgacgcc 600
gtcaccggca agttcacctg ccaggtgcct ggggtctact acttcgccgt ccatgccacc 660
gtctaccggg ccagcctgca gtttgatctg gtgaagaatg gcgaatccct tgcctctttc 720
ttccagtttt tcgggggtg gcccaagcca gcctcgctct cgggggggc catggtgagg 780

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ctggagcctg aggaccaagt gtgggtgcag gtgggtgtgg gtgactacat tggcatctat      840
gccagcatca agacagacag caccttctcc ggatttctgg tgtactccga ctggcacagc      900
tccccagtct ttgcttagtg cccactgcaa agtgagctca tgctctcact cctagaagga      960
gggtgtgagg ctgacaacct ggtcatccag gagggctggc cccctggaa tattgtgaat      1020
gactagggag gtggggtaga gcactctccg tcctgctgct ggcaaggaat gggaacagtg     1080
gctgtctgcg atcaggtctg gcagcatggg gcagtggctg gatttctgcc caagaccaga     1140
ggagtgtgct gtgctggcaa gtgtaagtcc cccagttgct ctggtccagg agcccacggt     1200
ggggtgctct cttcctggtc ctctgcttct ctggatcctc cccacccct cctgctcctg      1260
gggccggccc ttttctcaga gatcactcaa taaacctaag aaccctccaa aaaaaaaaaa     1320
aaaaaaaagg gcggccgc                                                   1338

<210> 110
<211> 406
<212> PRT
<213> Homo sapiens

<400> 110
Met Gly Pro Ser Thr Pro Leu Leu Ile Leu Phe Leu Leu Ser Trp Ser
 1               5                  10                  15
Gly Pro Leu Gln Gly Gln Gln His His Leu Val Glu Tyr Met Glu Arg
            20                  25                  30
Arg Leu Ala Ala Leu Glu Glu Arg Leu Ala Gln Cys Gln Asp Gln Ser
        35                  40                  45
Ser Arg His Ala Ala Glu Leu Arg Asp Phe Lys Asn Lys Met Leu Pro
    50                  55                  60
Leu Leu Glu Val Ala Glu Lys Glu Arg Glu Ala Leu Arg Thr Glu Ala
65                  70                  75                  80
Asp Thr Ile Ser Gly Arg Val Asp Arg Leu Glu Arg Glu Ala Asp Tyr
                85                  90                  95
Leu Glu Thr Gln Asn Pro Ala Leu Pro Cys Val Glu Phe Asp Glu Lys
            100                 105                 110
Val Thr Gly Gly Pro Gly Thr Lys Gly Lys Gly Arg Arg Asn Glu Lys
        115                 120                 125
Tyr Asp Met Val Thr Asp Cys Gly Tyr Thr Ile Ser Gln Val Arg Ser
    130                 135                 140
Met Lys Ile Leu Lys Arg Phe Gly Gly Pro Ala Gly Leu Trp Thr Lys
145                 150                 155                 160
Asp Pro Leu Gly Gln Thr Glu Lys Ile Tyr Val Leu Asp Gly Thr Gln
                165                 170                 175
Asn Asp Thr Ala Phe Val Phe Pro Arg Leu Arg Asp Phe Thr Leu Ala
            180                 185                 190
Met Ala Ala Arg Lys Ala Ser Arg Val Arg Val Pro Phe Pro Trp Val
        195                 200                 205
Gly Thr Gly Gln Leu Val Tyr Gly Gly Phe Leu Tyr Phe Ala Arg Arg
    210                 215                 220
Pro Pro Gly Arg Pro Gly Gly Gly Gly Glu Met Glu Asn Thr Leu Gln
225                 230                 235                 240
Leu Ile Lys Phe His Leu Ala Asn Arg Thr Val Val Asp Ser Ser Val
                245                 250                 255
Phe Pro Ala Glu Gly Leu Ile Pro Pro Tyr Gly Leu Thr Ala Asp Thr
            260                 265                 270
Tyr Ile Asp Leu Ala Ala Asp Glu Glu Gly Leu Trp Ala Val Tyr Ala
        275                 280                 285
Thr Arg Glu Asp Asp Arg His Leu Cys Leu Ala Lys Leu Asp Pro Gln
    290                 295                 300
Thr Leu Asp Thr Glu Gln Gln Trp Asp Thr Pro Cys Pro Arg Glu Asn
305                 310                 315                 320
Ala Glu Ala Ala Phe Val Ile Cys Gly Thr Leu Tyr Val Val Tyr Asn
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325 330 335
Thr Arg Pro Ala Ser Arg Ala Arg Ile Gln Cys Ser Phe Asp Ala Ser
340 345 350
Gly Thr Leu Thr Pro Glu Arg Ala Ala Leu Pro Tyr Phe Pro Arg Arg
355 360 365
Tyr Gly Ala His Ala Ser Leu Arg Tyr Asn Pro Arg Glu Arg Gln Leu
370 375 380
Tyr Ala Trp Asp Asp Gly Tyr Gln Ile Val Tyr Lys Leu Glu Met Arg
385 390 395 400
Lys Lys Glu Glu Glu Val
405

<210> 111
<211> 1831
<212> DNA
<213> Homo sapiens

<400> 111
gtcgacccac gcgtccgcgg acgcgtgggt gaggggaaga ggctgactgt acgttccttc 60
tactctggca ccactctcca ggctgccatg ggcccagca cccctctcct catcttgttc 120
cttttgtcat ggtcgggacc cctccaagga cagcagcacc accttgtgga gtacatggaa 180
cgccgactag ctgctttaga ggaacggctg gcccagtgcc aggaccagag tagtcggcat 240
gctgctgagc tgcgggactt caagaacaag atgctgccac tgctggaggt ggcagagaag 300
gagcgggagg cactcagaac tgaggccgac accatctccg ggagagtgga tcgtctggag 360
cgggaggcag actatctgga gacccagaac ccagctctgc cctgtgtaga gtttgatgag 420
aaggtgactg gaggccctgg gaccaaaggc aagggaagaa ggaatgagaa gtacgatatg 480
gtgacagact gtggctacac aatctctcaa gtgagatcaa tgaagattct gaagcgattt 540
ggtggcccag ctggtctatg gaccaaggat ccactggggc aaacagagaa gatctacgtg 600
ttagatggga cacagaatga cacagccttt gtcttcccaa ggctgcgtga cttcaccctt 660
gccatggctg cccggaaagc ttcccgagtc cgggtgccct tcccctgggt aggcacaggg 720
cagctggtat atggtggctt tctttatttt gctcggaggc ctcctggaag acctggtgga 780
ggtggtgaga tggagaacac tttgcagcta atcaaattcc acctggcaaa ccgaacagtg 840
gtggacagct cagtattccc agcagagggg ctgatccccc cctacggctt gacagcagac 900
acctacatcg acctggcagc tgatgaggaa ggtctttggg ctgtctatgc cacccgggag 960
gatgacaggc acttgtgtct ggccaagtta gatccacaga cactggacac agagcagcag 1020
tgggacacac catgtcccag agagaatgct gaggctgcct ttgtcatctg tgggaccctc 1080
tatgtcgtct ataacacccg tcctgccagt cgggcccgca tccagtgctc ctttgatgcc 1140
agcggcaccc tgacccctga acgggcagca ctcccttatt ttccccgcag atatggtgcc 1200
catgccagcc tccgctataa cccccgagaa cgccagctct atgcctggga tgatggctac 1260
cagattgtct ataagctgga gatgaggaag aaagaggagg aggtttgagg agctagcctt 1320
gtttttgca tctttctcac tcccatacat ttatattata tccccactaa atttcttgtt 1380
cctcattctt caaatgtggg ccagttgtgg ctcaaatcct ctatattttt agccaatggc 1440
aatcaaattc tttcagctcc tttgtttcat acggaactcc agatcctgag taatcctttt 1500
agagcccgaa gagtcaaaac cctcaatgtt ccctcctgct ctcctgcccc atgtcaacaa 1560
atttcaggct aaggatgccc cagacccagg gctctaacct tgtatgcggg caggcccagg 1620
gagcaggcag cagtgttctt cccctcagag tgacttgggg agggagaaat aggaggagac 1680
gtccagctct gtcctctctt cctcactcct cccttcagtg tcctgaggaa caggactttc 1740
tccacattgt tttgtattgc aacattttgc attaaaagga aaatccactg ctaaaaaaaa 1800
aaaaaaaaaa aaaaaaaaaa agggcggccg c 1831

<210> 112
<211> 406
<212> PRT
<213> Homo sapiens

<400> 112
Met Gly Pro Ser Thr Pro Leu Leu Ile Leu Phe Leu Leu Ser Trp Ser
1 5 10 15

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Gly Pro Leu Gln Gly Gln Gln His His Leu Val Glu Tyr Met Glu Arg
            20                  25                  30
Arg Leu Ala Ala Leu Glu Glu Arg Leu Ala Gln Cys Gln Asp Gln Ser
        35                  40                  45
Ser Arg His Ala Ala Glu Leu Arg Asp Phe Lys Asn Lys Met Leu Pro
    50                  55                  60
Leu Leu Glu Val Ala Glu Lys Glu Arg Glu Ala Leu Arg Thr Glu Ala
65                  70                  75                  80
Asp Thr Ile Ser Gly Arg Val Asp Arg Leu Glu Arg Glu Val Asp Tyr
                85                  90                  95
Leu Glu Thr Gln Asn Pro Ala Leu Pro Cys Val Glu Phe Asp Glu Lys
            100                 105                 110
Val Thr Gly Gly Pro Gly Thr Lys Gly Lys Gly Arg Arg Asn Glu Lys
        115                 120                 125
Tyr Asp Ile Val Thr Asp Cys Gly Tyr Thr Ile Ser Gln Val Arg Ser
    130                 135                 140
Met Lys Ile Leu Lys Arg Phe Gly Gly Pro Ala Gly Leu Trp Thr Lys
145                 150                 155                 160
Asp Pro Leu Gly Gln Thr Glu Lys Ile Tyr Val Leu Asp Gly Thr Gln
                165                 170                 175
Asn Asp Thr Ala Phe Val Phe Pro Arg Leu Arg Asp Phe Thr Leu Ala
            180                 185                 190
Met Ala Ala Arg Lys Ala Ser Arg Val Arg Val Pro Phe Pro Trp Val
        195                 200                 205
Gly Thr Gly Gln Leu Val Tyr Gly Gly Phe Leu Tyr Phe Ala Arg Arg
    210                 215                 220
Pro Pro Gly Arg Pro Gly Gly Gly Gly Glu Met Glu Asn Thr Leu Gln
225                 230                 235                 240
Leu Ile Lys Phe His Leu Ala Asn Arg Thr Val Val Asp Ser Ser Val
                245                 250                 255
Phe Pro Ala Glu Gly Leu Ile Pro Pro Tyr Gly Leu Thr Ala Asp Thr
            260                 265                 270
Tyr Ile Asp Leu Ala Ala Asp Glu Glu Gly Leu Trp Ala Val Tyr Ala
        275                 280                 285
Thr Arg Glu Asp Asp Arg His Leu Cys Leu Ala Lys Leu Asp Pro Gln
    290                 295                 300
Thr Leu Asp Thr Glu Gln Gln Trp Asp Thr Pro Cys Pro Arg Glu Asn
305                 310                 315                 320
Ala Glu Ala Ala Phe Val Ile Cys Gly Thr Leu Tyr Val Val Tyr Asn
                325                 330                 335
Thr Arg Pro Ala Ser Arg Ala Arg Ile Gln Cys Ser Phe Asp Ala Ser
            340                 345                 350
Gly Thr Leu Thr Pro Glu Arg Ala Ala Leu Pro Tyr Phe Pro Arg Arg
        355                 360                 365
Tyr Gly Ala His Ala Ser Leu Arg Tyr Asn Pro Arg Glu Arg Gln Leu
    370                 375                 380
Tyr Ala Trp Asp Asp Gly Tyr Gln Ile Val Tyr Lys Leu Glu Met Arg
385                 390                 395                 400
Lys Lys Glu Glu Glu Val
                405
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<210> 113
<211> 1831
<212> DNA
<213> Homo sapiens

<400> 113
gtcgacccac gcgtccgcgg acgcgtgggt gaggggaaga ggctgactgt acgttccttc 60

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tactctggca ccactctcca ggctgccatg gggcccagca cccctctcct catcttgttc      120
cttttgtcat ggtcgggacc cctccaagga cagcagcacc accttgtgga gtacatggaa      180
cgccgactag ctgctttaga ggaacggctg gcccagtgcc aggaccagag tagtcggcat      240
gctgctgagc tgcgggactt caagaacaag atgctgccac tgctggaggt ggcagagaag      300
gagcgggagg cactcagaac tgaggccgac accatctccg ggagagtgga tcgtctggag      360
cgggaggtag actatctgga gacccagaac ccagctctgc cctgtgtaga gtttgatgag      420
aaggtgactg gaggccctgg gaccaaaggc aagggaagaa ggaatgagaa gtacgatata      480
gtgacagact gtggctacac aatctctcaa gtgagatcaa tgaagattct gaagcgattt      540
ggtggcccag ctggtctatg gaccaaggat ccactggggc aaacagagaa gatctacgtg      600
ttagatggga cacagaatga cacagccttt gtcttcccaa ggctgcgtga cttcaccctt      660
gccatggctg cccggaaagc ttcccgagtc cgggtgccct tcccctgggt aggcacaggg      720
cagctggtat atggtggctt tctttatttt gctcggaggc ctcctggaag acctggtgga      780
ggtggtgaga tggagaacac tttgcagcta atcaaattcc acctggcaaa ccgaacagtg      840
gtggacagct cagtattccc agcagagggg ctgatccccc cctacggctt gacagcagac      900
acctacatcg acctggcagc tgatgaggaa ggtctttggg ctgtctatgc cacccgggag      960
gatgacaggc acttgtgtct ggccaagtta gatccacaga cactggacac agagcagcag     1020
tgggacacac catgtcccag agagaatgct gaggctgcct ttgtcatctg tgggaccctc     1080
tatgtcgtct ataacacccg tcctgccagt cgggcccgca tccagtgctc ctttgatgcc     1140
agcggcaccc tgacccctga acgggcagca ctcccttatt ttccccgcag atatggtgcc     1200
catgccagcc tccgctataa cccccgagaa cgccagctct atgcctggga tgatggctac     1260
cagattgtct ataagctgga gatgaggaag aaagaggagg aggtttgagg agctagcctt     1320
gtttttgca tctttctcac tcccatacat ttatattata tccccactaa atttcttgtt     1380
cctcattctt caaatgtggg ccagttgtgg ctcaaatcct ctatattttt agccaatggc     1440
aatcaaattc tttcagctcc tttgtttcat acggaactcc agatcctgag taatcctttt     1500
agagcccgaa gagtcaaaac cctcaatgtt ccctcctgct ctcctgcccc atgtcaacaa     1560
atttcaggct aaggatgccc cagacccagg gctctaacct tgtatgcggg caggcccagg     1620
gagcaggcag cagtgttctt cccctcagag tgacttgggg agggagaaat aggaggagac     1680
gtccagctct gtcctctctt cctcactcct cccttcagtg tcctgaggaa caggactttc     1740
tccacattgt tttgtattgc aacattttgc attaaaagga aaatccactg ctaaaaaaaa     1800
aaaaaaaaaa aaaaaaaaaa agggcggccg c                                    1831
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<210> 114
<211> 406
<212> PRT
<213> Homo sapiens

<400> 114

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Met Gly Pro Ser Thr Pro Leu Leu Ile Leu Phe Leu Leu Ser Trp Ser
 1               5                  10                  15
Gly Pro Leu Gln Gly Gln Gln His His Leu Val Glu Tyr Met Glu Arg
            20                  25                  30
Arg Leu Ala Ala Leu Glu Glu Arg Leu Ala Gln Cys Gln Asp Gln Ser
        35                  40                  45
Ser Arg His Ala Ala Glu Leu Arg Asp Phe Lys Asn Lys Met Leu Pro
    50                  55                  60
Leu Leu Glu Val Ala Glu Lys Glu Arg Glu Ala Leu Arg Thr Glu Ala
65                  70                  75                  80
Asp Thr Ile Ser Gly Arg Val Asp Arg Leu Glu Arg Glu Val Asp Tyr
                85                  90                  95
Leu Glu Thr Gln Asn Pro Ala Leu Pro Cys Val Glu Phe Asp Glu Lys
            100                 105                 110
Val Thr Gly Gly Pro Gly Thr Lys Gly Lys Gly Arg Arg Asn Glu Lys
        115                 120                 125
Tyr Asp Met Val Thr Asp Cys Gly Tyr Thr Ile Ser Gln Val Arg Ser
    130                 135                 140
Met Lys Ile Leu Lys Arg Phe Gly Gly Pro Ala Gly Ile Trp Thr Lys
145                 150                 155                 160
Asp Pro Leu Gly Gln Thr Glu Lys Ile Tyr Val Leu Asp Gly Thr Gln
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                165                 170                 175
Asn Asp Thr Ala Phe Val Phe Pro Arg Leu Arg Asp Phe Thr Leu Ala
            180                 185                 190
Met Ala Ala Arg Lys Ala Ser Arg Val Arg Val Pro Phe Pro Trp Val
        195                 200                 205
Gly Thr Gly Gln Leu Val Tyr Gly Gly Phe Leu Tyr Phe Ala Arg Arg
    210                 215                 220
Pro Pro Gly Arg Pro Gly Gly Gly Gly Glu Met Glu Asn Thr Leu Gln
225                 230                 235                 240
Leu Ile Lys Phe His Leu Ala Asn Arg Thr Val Val Asp Ser Ser Val
                245                 250                 255
Phe Pro Ala Glu Gly Leu Ile Pro Pro Tyr Gly Leu Thr Ala Asp Thr
            260                 265                 270
Tyr Ile Asp Leu Ala Ala Asp Glu Glu Gly Leu Trp Ala Val Tyr Ala
        275                 280                 285
Thr Arg Glu Asp Asp Arg His Leu Cys Leu Ala Lys Leu Asp Pro Gln
    290                 295                 300
Thr Leu Asp Thr Glu Gln Gln Trp Asp Thr Pro Cys Pro Arg Glu Asn
305                 310                 315                 320
Ala Glu Ala Ala Phe Val Ile Cys Gly Thr Leu Tyr Val Val Tyr Asn
                325                 330                 335
Thr Arg Pro Ala Ser Arg Ala Arg Ile Gln Cys Ser Phe Asp Ala Ser
            340                 345                 350
Gly Thr Leu Thr Pro Glu Arg Ala Ala Leu Pro Tyr Phe Pro Arg Arg
        355                 360                 365
Tyr Gly Ala His Ala Ser Leu Arg Tyr Asn Pro Arg Glu Arg Gln Leu
    370                 375                 380
Tyr Ala Trp Asp Asp Gly Tyr Gln Ile Val Tyr Lys Leu Glu Met Arg
385                 390                 395                 400
Lys Lys Glu Glu Glu Val
                405
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<210> 115
<211> 1831
<212> DNA
<213> Homo sapiens

<400> 115

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gtcgacccac gcgtccgcgg acgcgtgggt gaggggaaga ggctgactgt acgttccttc     60
tactctggca ccactctcca ggctgccatg gggcccagca cccctctcct catcttgttc    120
cttttgtcat ggtcgggacc cctccaagga cagcagcacc accttgtgga gtacatggaa    180
cgccgactag ctgctttaga ggaacggctg gcccagtgcc aggaccagag tagtcggcat    240
gctgctgagc tgcgggactt caagaacaag atgctgccac tgctggaggt ggcagagaag    300
gagcgggagg cactcagaac tgaggccgac accatctccg ggagagtgga tcgtctggag    360
cgggaggtag actatctgga gacccagaac ccagctctgc cctgtgtaga gtttgatgag    420
aaggtgactg gaggccctgg gaccaaaggc aagggaagaa ggaatgagaa gtacgatatg    480
gtgacagact gtggctacac aatctctcaa gtgagatcaa tgaagattct gaagcgattt    540
ggtggcccag ctggtatatg gaccaaggat ccactggggc aaacagagaa gatctacgtg    600
ttagatggga cacagaatga cacagccttt gtcttcccaa ggctgcgtga cttcaccctt    660
gccatggctg cccggaaagc ttcccgagtc cgggtgccct tcccctgggt aggcacaggg    720
cagctggtat atggtggctt tctttatttt gctcggaggc ctcctggaag acctggtgga    780
ggtggtgaga tggagaacac tttgcagcta atcaaattcc acctggcaaa ccgaacagtg    840
gtggacagct cagtattccc agcagagggg ctgatccccc cctacggctt gacagcagac    900
acctacatcg acctggcagc tgatgaggaa ggtctttggg ctgtctatgc cacccgggag    960
gatgacaggc acttgtgtct ggccaagtta gatccacaga cactggacac agagcagcag   1020
tgggacacac catgtcccag agagaatgct gaggctgcct ttgtcatctg tgggaccctc   1080
tatgtcgtct ataacacccg tcctgccagt cgggcccgca tccagtgctc ctttgatgcc   1140
agcggcaccc tgacccctga acgggcagca ctcccttatt ttccccgcag atatggtgcc   1200
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catgccagcc tccgctataa cccccgagaa cgccagctct atgcctggga tgatggctac     1260
cagattgtct ataagctgga gatgaggaag aaagaggagg aggtttgagg agctagcctt     1320
gtttttgca tctttctcac tcccatacat ttatattata tccccactaa atttcttgtt      1380
cctcattctt caaatgtggg ccagttgtgg ctcaaatcct ctatattttt agccaatggc     1440
aatcaaattc tttcagctcc tttgtttcat acggaactcc agatcctgag taatcctttt     1500
agagcccgaa gagtcaaaac cctcaatgtt ccctcctgct ctcctgcccc atgtcaacaa     1560
atttcaggct aaggatgccc cagacccagg gctctaacct tgtatgcggg caggcccagg     1620
gagcaggcag cagtgttctt cccctcagag tgacttgggg agggagaaat aggaggagac     1680
gtccagctct gtcctctctt cctcactcct cccttcagtg tcctgaggaa caggactttc     1740
tccacattgt tttgtattgc aacattttgc attaaaagga aaatccactg ctaaaaaaaa     1800
aaaaaaaaaa aaaaaaaaaa agggcggccg c                                    1831
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<210> 116
<211> 406
<212> PRT
<213> Homo sapiens

<400> 116

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Met Gly Pro Ser Thr Pro Leu Leu Ile Leu Phe Leu Leu Ser Trp Ser
1               5                   10                  15
Gly Pro Leu Gln Gly Gln Gln His His Leu Val Glu Tyr Met Glu Arg
            20                  25                  30
Arg Leu Ala Ala Leu Glu Glu Arg Leu Ala Gln Cys Gln Asp Gln Ser
        35                  40                  45
Ser Arg His Ala Ala Glu Leu Arg Asp Phe Lys Asn Lys Met Leu Pro
    50                  55                  60
Leu Leu Glu Val Ala Glu Lys Glu Arg Glu Ala Leu Arg Thr Glu Ala
65                  70                  75                  80
Asp Thr Ile Ser Gly Arg Val Asp Arg Leu Glu Arg Glu Val Asp Tyr
                85                  90                  95
Leu Glu Thr Gln Asn Pro Ala Leu Pro Cys Val Glu Phe Asp Glu Lys
            100                 105                 110
Val Thr Gly Gly Pro Gly Thr Lys Gly Lys Gly Arg Arg Asn Glu Lys
        115                 120                 125
Tyr Asp Met Val Thr Asp Cys Gly Tyr Thr Ile Ser Gln Val Arg Ser
    130                 135                 140
Met Lys Ile Leu Lys Arg Phe Gly Gly Pro Ala Gly Leu Trp Thr Lys
145                 150                 155                 160
Asp Pro Leu Gly Gln Thr Glu Lys Ile Tyr Val Leu Asp Gly Thr Gln
                165                 170                 175
Asn Asp Thr Val Phe Val Phe Pro Arg Leu Arg Asp Phe Thr Leu Ala
            180                 185                 190
Met Ala Ala Arg Lys Ala Ser Arg Val Arg Val Pro Phe Pro Trp Val
        195                 200                 205
Gly Thr Gly Gln Leu Val Tyr Gly Gly Phe Leu Tyr Phe Ala Arg Arg
    210                 215                 220
Pro Pro Gly Arg Pro Gly Gly Gly Gly Glu Met Glu Asn Thr Leu Gln
225                 230                 235                 240
Leu Ile Lys Phe His Leu Ala Asn Arg Thr Val Val Asp Ser Ser Val
                245                 250                 255
Phe Pro Ala Glu Gly Leu Ile Pro Pro Tyr Gly Leu Thr Ala Asp Thr
            260                 265                 270
Tyr Ile Asp Leu Ala Ala Asp Glu Glu Gly Leu Trp Ala Val Tyr Ala
        275                 280                 285
Thr Arg Glu Asp Asp Arg His Leu Cys Leu Ala Lys Leu Asp Pro Gln
    290                 295                 300
Thr Leu Asp Thr Glu Gln Gln Trp Asp Thr Pro Cys Pro Arg Glu Asn
305                 310                 315                 320
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Ala Glu Ala Ala Phe Val Ile Cys Gly Thr Leu Tyr Val Val Tyr Asn
325 330 335
Thr Arg Pro Ala Ser Arg Ala Arg Ile Gln Cys Ser Phe Asp Ala Ser
340 345 350
Gly Thr Leu Thr Pro Glu Arg Ala Ala Leu Pro Tyr Phe Pro Arg Arg
355 360 365
Tyr Gly Ala His Ala Ser Leu Arg Tyr Asn Pro Arg Glu Arg Gln Leu
370 375 380
Tyr Ala Trp Asp Asp Gly Tyr Gln Ile Val Tyr Lys Leu Glu Met Arg
385 390 395 400
Lys Lys Glu Glu Glu Val
405

<210> 117
<211> 1831
<212> DNA
<213> Homo sapiens

<400> 117
gtcgacccac gcgtccgcgg acgcgtgggt gaggggaaga ggctgactgt acgttccttc 60
tactctggca ccactctcca ggctgccatg gggcccagca cccctctcct catcttgttc 120
cttttgtcat ggtcgggacc cctccaagga cagcagcacc accttgtgga gtacatggaa 180
cgccgactag ctgctttaga ggaacggctg gcccagtgcc aggaccagag tagtcggcat 240
gctgctgagc tgcgggactt caagaacaag atgctgccac tgctggaggt ggcagagaag 300
gagcgggagg cactcagaac tgaggccgac accatctccg ggagagtgga tcgtctggag 360
cgggaggtag actatctgga gacccagaac ccagctctgc cctgtgtaga gtttgatgag 420
aaggtgactg gaggccctgg gaccaaaggc aagggaagaa ggaatgagaa gtacgatatg 480
gtgacagact gtggctacac aatctctcaa gtgagatcaa tgaagattct gaagcgattt 540
ggtggcccag ctggtctatg gaccaaggat ccactggggc aaacagagaa gatctacgtg 600
ttagatggga cacagaatga cacagtcttt gtcttcccaa ggctgcgtga cttcaccctt 660
gccatggctg cccggaaagc ttcccgagtc cgggtgccct tcccctgggt aggcacaggg 720
cagctggtat atggtggctt tctttatttt gctcggaggc ctcctggaag acctggtgga 780
ggtggtgaga tggagaacac tttgcagcta atcaaattcc acctggcaaa ccgaacagtg 840
gtggacagct cagtattccc agcagagggg ctgatccccc cctacggctt gacagcagac 900
acctacatcg acctggcagc tgatgaggaa ggtctttggg ctgtctatgc cacccgggag 960
gatgacaggc acttgtgtct ggccaagtta gatccacaga cactggacac agagcagcag 1020
tgggacacac catgtcccag agagaatgct gaggctgcct ttgtcatctg tgggaccctc 1080
tatgtcgtct ataacacccg tcctgccagt cgggcccgca tccagtgctc ctttgatgcc 1140
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catgccagcc tccgctataa cccccgagaa cgccagctct atgcctggga tgatggctac 1260
cagattgtct ataagctgga gatgaggaag aaagaggagg aggtttgagg agctagcctt 1320
gtttttgca tctttctcac tcccatacat ttatattata tccccactaa atttcttgtt 1380
cctcattctt caaatgtggg ccagttgtgg ctcaaatcct ctatattttt agccaatggc 1440
aatcaaattc tttcagctcc tttgtttcat acggaactcc agatcctgag taatcctttt 1500
agagcccgaa gagtcaaaac cctcaatgtt ccctcctgct ctcctgcccc atgtcaacaa 1560
atttcaggct aaggatgccc cagacccagg gctctaacct tgtatgcggg caggcccagg 1620
gagcaggcag cagtgttctt cccctcagag tgacttgggg agggagaaat aggaggagac 1680
gtccagctct gtcctctctt cctcactcct cccttcagtg tcctgaggaa caggactttc 1740
tccacattgt tttgtattgc aacattttgc attaaaagga aaatccactg ctaaaaaaaa 1800
aaaaaaaaaa aaaaaaaaaa agggcggccg c 1831

<210> 118
<211> 242
<212> PRT
<213> Mus musculus

<400> 118
Met Arg Pro Leu Leu Ala Leu Leu Leu Leu Gly Leu Val Ser Gly Ser

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 1               5                   10                  15
Pro Pro Leu Asp Asp Asn Lys Ile Pro Ser Leu Cys Pro Gly Gln Pro
            20                  25                  30
Gly Leu Pro Gly Thr Pro Gly His His Gly Ser Gln Gly Leu Pro Gly
        35                  40                  45
Arg Asp Gly Arg Asp Gly Arg Asp Gly Ala Pro Gly Ala Pro Gly Glu
    50                  55                  60
Lys Gly Glu Gly Gly Arg Pro Gly Leu Pro Gly Pro Arg Gly Glu Pro
65                  70                  75                  80
Gly Pro Arg Gly Glu Gly Pro Met Gly Ala Ile Gly Pro Ala Gly Glu
                85                  90                  95
Cys Ser Val Pro Pro Arg Ser Ala Phe Ser Ala Lys Arg Ser Glu Ser
            100                 105                 110
Arg Val Pro Pro Pro Ala Asp Thr Pro Leu Pro Phe Asp Arg Val Leu
        115                 120                 125
Leu Asn Glu Gln Gly His Tyr Asp Pro Thr Thr Gly Lys Phe Thr Cys
    130                 135                 140
Gln Val Pro Gly Val Tyr Tyr Phe Ala Val His Ala Thr Val Tyr Arg
145                 150                 155                 160
Ala Ser Leu Gln Phe Asp Leu Val Lys Asn Gly Gln Ser Ile Ala Ser
                165                 170                 175
Phe Phe Gln Tyr Phe Gly Gly Trp Pro Lys Pro Ala Ser Leu Ser Gly
            180                 185                 190
Gly Ala Met Val Arg Leu Glu Pro Glu Asp Gln Val Trp Val Gln Val
        195                 200                 205
Gly Val Gly Asp Tyr Ile Gly Ile Tyr Ala Ser Ile Lys Thr Asp Ser
    210                 215                 220
Thr Phe Ser Gly Phe Leu Val Tyr Ser Asp Trp His Ser Ser Pro Val
225                 230                 235                 240
Phe Ala
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<210> 119
<211> 1263
<212> DNA
<213> Mus musculus

<400> 119

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cagcaaggac aggggctgcc tgcctacaga ctacaagaga ggttcctgga gtctgagcct     120
ccggggtcac caccatgagg ccacttcttg cccttctgct tctgggtctg gtgtcaggct     180
ctcctcctct ggacgacaac aagatcccca gcctgtgtcc cgggcagccc ggccttccag     240
gcacaccagg tcaccatggc agccaaggcc tgcctggccg tgacggccgt gatggccgcg     300
acggtgcacc cggagctccg ggagagaaag gcgagggcgg gagaccggga ctacctggcc     360
cacgtgggga gcccgggccg cgtggagagg tagggcccat gggggctatc gggcctgcgg     420
gggagtgctc ggtacccccca cgatcagcct tcagtgccaa gcgatccgag agccgggtac     480
ctccgccagc cgacacaccc ctacctttcg accgtgtgct gctaaatgag cagggccatt     540
acgaccccac tactggcaag ttcacctgcc aagtgcctgg cgtctactac tttgctgtgc     600
acgccactgt ctaccgggcc agcttgcagt ttgatcttgt caaaaacggg cagtccatcg     660
cctctttctt ccagtatttt ggggggtggc ccaagccagc ctcgctctca gggggtgcga     720
tggtaaggct agaacctgag gaccaggtgt gggtgcaggt gggcgtgggt gattacattg     780
gcatctatgc cagcatcaag acagacagta ccttctctgg atttctcgtc tattctgact     840
ggcacagctc cccagtcttc gcttaaaaca cagtgaaccc ggagctggca cttgctcctc     900
agtggagggt gtgacactaa cccgcgcagc gcataccagg agggctggcc ccctggaata     960
ttgtgaatga cttaggaaga gagggagcca cttccagtcc cactgctggc aatgaatgga    1020
gacaggctgt ctgaggtcaa gacagcgtgg agcagtggct gggtttctgc ccaggacttt    1080
agaatgcagt aggctggcag ctgtgggtcc tggcccagga ctccaaggtg ggatgctcca    1140
ttcctagtcc tgtgtcccct ctaggtccct gactccatct ctgctgctcc cagggcaggc    1200
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cttttctca gaggtcactt aataaaccta aaatcctcaa aaaaaaaaa aaagggcggc 1260
cgc 1263

<210> 120
<211> 243
<212> PRT
<213> Mus musculus

<400> 120
Met Arg Pro Leu Leu Ala Leu Leu Leu Leu Gly Leu Val Ser Gly Ser
1 5 10 15
Pro Pro Leu Asp Asp Asn Lys Ile Pro Ser Leu Cys Pro Gly Gln Pro
20 25 30
Gly Leu Pro Gly Thr Pro Gly His His Gly Ser Gln Gly Leu Pro Gly
35 40 45
Arg Asp Gly Arg Asp Gly Arg Asp Gly Ala Pro Gly Ala Pro Gly Glu
50 55 60
Lys Gly Glu Gly Gly Arg Pro Gly Leu Pro Gly Pro Arg Gly Glu Pro
65 70 75 80
Gly Pro Arg Gly Glu Ala Gly Pro Met Gly Ala Ile Gly Pro Ala Gly
85 90 95
Glu Cys Ser Val Pro Pro Arg Ser Ala Phe Ser Val Lys Arg Ser Glu
100 105 110
Ser Arg Val Pro Pro Pro Ala Asp Thr Pro Leu Pro Phe Asp Arg Val
115 120 125
Leu Leu Asn Glu Gln Gly His Tyr Asp Pro Thr Thr Gly Lys Phe Thr
130 135 140
Cys Gln Val Pro Gly Val Tyr Tyr Phe Ala Val His Ala Thr Val Tyr
145 150 155 160
Arg Ala Ser Leu Gln Phe Asp Leu Val Lys Asn Gly Gln Ser Ile Ala
165 170 175
Ser Phe Phe Gln Tyr Phe Gly Gly Trp Pro Lys Pro Ala Ser Leu Ser
180 185 190
Gly Gly Ala Met Val Arg Leu Glu Pro Glu Asp Gln Val Trp Val Gln
195 200 205
Val Gly Val Gly Asp Tyr Ile Gly Ile Tyr Ala Ser Ile Lys Thr Asp
210 215 220
Ser Thr Phe Ser Gly Phe Leu Val Tyr Ser Asp Trp His Ser Ser Pro
225 230 235 240
Val Phe Ala

<210> 121
<211> 1263
<212> DNA
<213> Mus musculus

<400> 121
gtcgacccac gcgtccgcgc tgtgaagcca gcaaggagca accagaagct aggagtcagt 60
cagcaaggac aggggctgcc tgcctacaga ctacaagaga ggttcctgga gtctgagcct 120
ccggggtcac caccatgagg ccacttcttg cccttctgct tctgggtctg gtgtcaggct 180
ctcctcctct ggacgacaac aagatcccca gcctgtgtcc cgggcagccc ggccttccag 240
gcacaccagg tcaccatggc agccaaggcc tgcctggccg tgacggccgt gatggccgcg 300
acggtgcacc cggagctccg ggagagaaag gcgagggcgg gagaccggga ctacctggcc 360
cacgtgggga gcccgggccg cgtggagagg cagggcccat gggggctatc gggcctgcgg 420
gggagtgctc ggtacccccca cgatcagtct tcagtgccaa gcgatccgag agccgggtac 480
ctccgccagc cgacacaccc ctacctttcg accgtgtgct gctaaatgag cagggccatt 540
acgaccccac tactggcaag ttcacctgcc aagtgcctgg cgtctactac tttgctgtgc 600

acgccactgt ctaccgggcc agcttgcagt ttgatcttgt caaaaacggg cagtccatcg 660
cctctttctt ccagtatttt gggggtggc ccaagccagc ctcgctctca gggggtgcga 720
tggtaaggct agaacctgag gaccaggtgt gggtgcaggt gggcgtgggt gattacattg 780
gcatctatgc cagcatcaag acagacagta ccttctctgg atttctcgtc tattctgact 840
ggcacagctc cccagtcttc gcttaaaaca cagtgaaccc ggagctggca cttgctcctc 900
agtggagggt gtgacactaa cccgcgcagc gcataccagg agggctggcc ccctggaata 960
ttgtgaatga cttaggaaga gagggagcca cttccagtcc cactgctggc aatgaatgga 1020
gacaggctgt ctgaggtcaa gacagcgtgg agcagtggct gggtttctgc ccaggacttt 1080
agaatgcagt aggctggcag ctgtgggtcc tggcccagga ctccaaggtg ggatgctcca 1140
ttcctagtcc tgtgtcccct ctaggtccct gactccatct ctgctgctcc cagggcaggc 1200
ctttttctca gaggtcactt aataaaccta aaatcctcaa aaaaaaaaaa aaagggcggc 1260
cgc 1263

<210> 122
<211> 243
<212> PRT
<213> Mus musculus

<400> 122
Met Arg Pro Leu Leu Ala Leu Leu Leu Leu Gly Leu Val Ser Gly Ser
1 5 10 15
Pro Pro Leu Asp Asp Asn Lys Ile Pro Ser Leu Cys Pro Gly Gln Pro
20 25 30
Gly Leu Pro Gly Thr Pro Gly His His Gly Ser Gln Gly Leu Pro Gly
35 40 45
Arg Asp Gly Arg Asp Gly Arg Asp Gly Ala Pro Gly Ala Pro Gly Glu
50 55 60
Lys Gly Glu Gly Gly Arg Pro Gly Leu Pro Gly Pro Arg Gly Glu Pro
65 70 75 80
Gly Pro Arg Gly Glu Ala Gly Pro Met Gly Ala Ile Gly Pro Ala Gly
85 90 95
Glu Cys Ser Val Pro Pro Arg Ser Ala Phe Ser Ala Lys Arg Ser Glu
100 105 110
Ser Arg Val Pro Pro Pro Ala Asp Thr Pro Leu Pro Phe Asp Arg Ala
115 120 125
Leu Leu Asn Glu Gln Gly His Tyr Asp Pro Thr Thr Gly Lys Phe Thr
130 135 140
Cys Gln Val Pro Gly Val Tyr Tyr Phe Ala Val His Ala Thr Val Tyr
145 150 155 160
Arg Ala Ser Leu Gln Phe Asp Leu Val Lys Asn Gly Gln Ser Ile Ala
165 170 175
Ser Phe Phe Gln Tyr Phe Gly Gly Trp Pro Lys Pro Ala Ser Leu Ser
180 185 190
Gly Gly Ala Met Val Arg Leu Glu Pro Glu Asp Gln Val Trp Val Gln
195 200 205
Val Gly Val Gly Asp Tyr Ile Gly Ile Tyr Ala Ser Ile Lys Thr Asp
210 215 220
Ser Thr Phe Ser Gly Phe Leu Val Tyr Ser Asp Trp His Ser Ser Pro
225 230 235 240
Val Phe Ala

<210> 123
<211> 1263
<212> DNA
<213> Mus musculus

<400> 123

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gtcgacccac gcgtccgcgc tgtgaagcca gcaaggagca accagaagct aggagtcagt     60
cagcaaggac aggggctgcc tgcctacaga ctacaagaga ggttcctgga gtctgagcct    120
ccggggtcac caccatgagg ccacttcttg cccttctgct tctgggtctg gtgtcaggct    180
ctcctcctct ggacgacaac aagatcccca gcctgtgtcc cgggcagccc ggccttccag    240
gcacaccagg tcaccatggc agccaaggcc tgcctggccg tgacggccgt gatggccgcg    300
acggtgcacc cggagctccg ggagagaaag gcgagggcgg gagaccggga ctacctggcc    360
cacgtgggga gcccggccg cgtggagagg cagggcccat gggggctatc gggcctgcgg     420
gggagtgctc ggtacccca cgatcagcct tcagtgccaa gcgatccgag agccgggtac     480
ctccgccagc cgacacaccc ctacctttcg accgtgcgct gctaaatgag cagggccatt    540
acgaccccac tactggcaag ttcacctgcc aagtgcctgg cgtctactac tttgctgtgc    600
acgccactgt ctaccgggcc agcttgcagt ttgatcttgt caaaaacggg cagtccatcg    660
cctctttctt ccagtatttt gggggggtggc ccaagccagc ctcgctctca gggggtgcga   720
tggtaaggct agaacctgag gaccaggtgt gggtgcaggt gggcgtgggt gattacattg    780
gcatctatgc cagcatcaag acagacagta ccttctctgg atttctcgtc tattctgact    840
ggcacagctc cccagtcttc gcttaaaaca cagtgaaccc ggagctggca cttgctcctc    900
agtggagggt gtgacactaa cccgcgcagc gcataccagg agggctggcc ccctggaata    960
ttgtgaatga cttaggaaga gagggagcca cttccagtcc cactgctggc aatgaatgga   1020
gacaggctgt ctgaggtcaa gacagcgtgg agcagtggct gggtttctgc ccaggacttt   1080
agaatgcagt aggctggcag ctgtgggtcc tggcccagga ctccaaggtg ggatgctcca   1140
ttcctagtcc tgtgtcccct ctaggtccct gactccatct ctgctgctcc cagggcaggc   1200
ctttttctca gaggtcactt aataaaccta aaatcctcaa aaaaaaaaaa aaagggcggc   1260
cgc                                                                 1263

<210> 124
<211> 243
<212> PRT
<213> Mus musculus

<400> 124
Met Arg Pro Leu Leu Ala Leu Leu Leu Leu Gly Leu Val Ser Gly Ser
 1               5                  10                  15
Pro Pro Leu Asp Asp Asn Lys Ile Pro Ser Leu Cys Pro Gly Gln Pro
            20                  25                  30
Gly Leu Pro Gly Thr Pro Gly His His Gly Ser Gln Gly Leu Pro Gly
        35                  40                  45
Arg Asp Gly Arg Asp Gly Arg Asp Gly Ala Pro Gly Ala Pro Gly Glu
    50                  55                  60
Lys Gly Glu Gly Gly Arg Pro Gly Leu Pro Gly Pro Arg Gly Glu Pro
65                  70                  75                  80
Gly Pro Arg Gly Glu Ala Gly Pro Met Gly Ala Ile Gly Pro Ala Gly
                85                  90                  95
Glu Cys Ser Val Pro Pro Arg Ser Ala Phe Ser Ala Lys Arg Ser Glu
            100                 105                 110
Ser Arg Val Pro Pro Pro Ala Asp Thr Pro Leu Pro Phe Asp Arg Val
        115                 120                 125
Leu Leu Asn Glu Gln Gly His Tyr Asp Pro Thr Thr Gly Lys Phe Thr
    130                 135                 140
Cys Gln Val Pro Gly Val Tyr Tyr Phe Ala Val His Ala Thr Val Tyr
145                 150                 155                 160
Arg Ala Ser Leu Gln Phe Asp Ile Val Lys Asn Gly Gln Ser Ile Ala
                165                 170                 175
Ser Phe Phe Gln Tyr Phe Gly Gly Trp Pro Lys Pro Ala Ser Leu Ser
            180                 185                 190
Gly Gly Ala Met Val Arg Leu Glu Pro Glu Asp Gln Val Trp Val Gln
        195                 200                 205
Val Gly Val Gly Asp Tyr Ile Gly Ile Tyr Ala Ser Ile Lys Thr Asp
    210                 215                 220
Ser Thr Phe Ser Gly Phe Leu Val Tyr Ser Asp Trp His Ser Ser Pro
```

```
225             230             235             240
Val Phe Ala
```

<210> 125
<211> 1263
<212> DNA
<213> Mus musculus

<400> 125
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gtcgacccac gcgtccgcgc tgtgaagcca gcaaggagca accagaagct aggagtcagt     60
cagcaaggac aggggctgcc tgcctacaga ctacaagaga ggttcctgga gtctgagcct    120
ccggggtcac caccatgagg ccacttcttg cccttctgct tctgggtctg gtgtcaggct    180
ctcctcctct ggacgacaac aagatcccca gcctgtgtcc cgggcagccc ggccttccag    240
gcacaccagg tcaccatggc agccaaggcc tgcctggccg tgacggccgt gatggccgcg    300
acggtgcacc cggagctccg ggagagaaag gcgagggcgg gagaccggga ctacctggcc    360
cacgtgggga gcccgggccg cgtggagagg cagggcccat gggggctatc gggcctgcgg    420
gggagtgctc ggtacccccca cgatcagcct tcagtgccaa gcgatccgag agccgggtac    480
ctccgccagc cgacacaccc ctacctttcg accgtgtgct gctaaatgag cagggccatt    540
acgaccccac tactggcaag ttcacctgcc aagtgcctgg cgtctactac tttgctgtgc    600
acgccactgt ctaccgggcc agcttgcagt ttgatattgt caaaaacggg cagtccatcg    660
cctctttctt ccagtatttt gggggggtggc ccaagccagc ctcgctctca ggggggtgcga    720
tggtaaggct agaacctgag gaccaggtgt gggtgcaggt gggcgtgggt gattacattg    780
gcatctatgc cagcatcaag acagacagta ccttctctgg atttctcgtc tattctgact    840
ggcacagctc cccagtcttc gcttaaaaca cagtgaaccc ggagctggca cttgctcctc    900
agtggagggt gtgacactaa cccgcgcagc gcataccagg agggctggcc ccctggaata    960
ttgtgaatga cttaggaaga gagggagcca cttccagtcc cactgctggc aatgaatgga   1020
gacaggctgt ctgaggtcaa gacagcgtgg agcagtggct gggtttctgc ccaggacttt   1080
agaatgcagt aggctggcag ctgtgggtcc tggcccagga ctccaaggtg ggatgctcca   1140
ttcctagtcc tgtgtcccct ctaggtccct gactccatct ctgctgctcc cagggcaggc   1200
ctttttctca gaggtcactt aataaaccta aaatcctcaa aaaaaaaaaa aaagggcggc   1260
cgc                                                                  1263
```

<210> 126
<211> 406
<212> PRT
<213> Mus musculus

<400> 126
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Met Gly Pro Ser Ala Pro Leu Leu Leu Leu Phe Phe Leu Ser Trp Thr
1               5                   10                  15
Gly Pro Leu Gln Gly Gln Gln His His Leu Val Glu Tyr Met Glu Arg
            20                  25                  30
Arg Leu Ala Ala Leu Glu Glu Arg Leu Ala Gln Cys Gln Asp Gln Ser
        35                  40                  45
Ser Arg His Ala Ala Glu Leu Arg Asp Phe Lys Asn Lys Met Leu Pro
    50                  55                  60
Leu Leu Glu Val Ala Glu Lys Glu Arg Glu Thr Leu Arg Thr Glu Ala
65                  70                  75                  80
Asp Ser Ile Ser Gly Arg Val Asp Arg Ile Glu Arg Glu Val Asp Tyr
                85                  90                  95
Leu Glu Thr Gln Asn Pro Ala Leu Pro Cys Val Glu Leu Asp Glu Lys
            100                 105                 110
Val Thr Gly Gly Pro Gly Ala Lys Gly Lys Gly Arg Arg Asn Glu Lys
        115                 120                 125
Tyr Asp Met Val Thr Asp Cys Ser Tyr Thr Val Ala Gln Val Arg Ser
    130                 135                 140
Met Lys Ile Leu Lys Arg Phe Gly Gly Ser Val Gly Leu Trp Thr Lys
```

```
145                 150                 155                 160
Asp Pro Leu Gly Pro Ala Glu Lys Ile Tyr Val Leu Asp Gly Thr Gln
                165                 170                 175
Asn Asp Thr Ala Phe Val Phe Pro Arg Leu Arg Asp Phe Thr Leu Ala
            180                 185                 190
Met Ala Ala Arg Lys Ala Ser Arg Ile Arg Val Pro Phe Pro Trp Val
        195                 200                 205
Gly Thr Gly Gln Leu Val Tyr Gly Gly Phe Leu Tyr Tyr Ala Arg Arg
    210                 215                 220
Pro Pro Gly Gly Pro Gly Gly Gly Gly Glu Leu Glu Asn Thr Leu Gln
225                 230                 235                 240
Leu Ile Lys Phe His Leu Ala Asn Arg Thr Val Val Asp Ser Ser Val
                245                 250                 255
Phe Pro Ala Glu Ser Leu Ile Pro Pro Tyr Gly Leu Thr Ala Asp Thr
            260                 265                 270
Tyr Ile Asp Leu Ala Ala Asp Glu Glu Gly Leu Trp Ala Val Tyr Ala
        275                 280                 285
Thr Arg Asp Asp Asp Arg His Leu Cys Leu Ala Lys Leu Asp Pro Gln
    290                 295                 300
Thr Leu Asp Thr Glu Gln Gln Trp Asp Thr Pro Cys Pro Arg Glu Asn
305                 310                 315                 320
Ala Glu Ala Ala Phe Val Ile Cys Gly Thr Leu Tyr Val Val Tyr Asn
                325                 330                 335
Thr Arg Pro Ala Ser Arg Ala Arg Ile Gln Cys Ser Phe Asp Ala Ser
            340                 345                 350
Gly Thr Leu Ala Pro Glu Arg Ala Ala Leu Ser Tyr Phe Pro Arg Arg
        355                 360                 365
Tyr Gly Ala His Ala Ser Leu Arg Tyr Asn Pro Arg Glu Arg Gln Leu
    370                 375                 380
Tyr Ala Trp Asp Asp Gly Tyr Gln Ile Val Tyr Lys Leu Glu Met Lys
385                 390                 395                 400
Lys Lys Glu Glu Glu Val
                405
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<210> 127
<211> 1721
<212> DNA
<213> Mus musculus

<400> 127

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gtcgacccac gcgtccgact taaggctgcc atggggccca gtgctcctct gctgctcctc     60
ttctttttgt catggacggg accccttcag ggacagcagc accaccttgt ggagtacatg    120
gaacgccgac tagctgcctt agaggaacgg ctggcccaat gccaggatca gagtagtcgg    180
catgctgccg agcttcggga cttcaaaaac aagatgttgc ctctcctgga ggtggcagag    240
aaggagcggg agaccctcag aactgaagca gactccatct caggaagagt ggaccgtatt    300
gaaagggagg tagactatct ggagacacag aacccagctt tgccctgtgt agagctggat    360
gagaaggtga ctggaggtcc tggagccaaa ggcaagggcc gaagaaatga gaaatacgat    420
atggtgacgg actgtagcta cacagtcgct caggtgaggt caatgaagat cctgaagcgg    480
tttggtggtt cagttggcct atggaccaag gatccgctgg ggccagcaga gaagatctac    540
gtgttagacg gcacccagaa cgacacggct tttgtcttcc caaggctgcg tgacttcacc    600
cttgccatgg ctgcccggaa agcttcccga attcgggtgc ccttcccctg ggtaggcacg    660
gggcagctgg tgtacggtgg cttcctttat tatgctcgaa ggcctcctgg aggacctgga    720
gggggtggtg aattggagaa cactctgcag ctgatcaaat ttcacttggc aaaccgaaca    780
gtggtggata gctcagtgtt ccctgcagag agcctgatac ccccctacgg cctgacagca    840
gatacatata tcgacctggc agctgatgag gagggcctgt gggctgtcta tgccactcga    900
gatgatgaca ggcatttgtg tctagccaag ttagacccac agacacttga cacagagcag    960
cagtgggaca caccatgtcc cagagagaac gcagaggctg cgtttgtcat ctgtgggacc   1020
ctgtacgttg tctataacac ccgccctgcc agtagggctc gtattcagtg ttccttcgat   1080
```

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gccagtggta ctctcgcccc tgaaagggca gcactctcct attttccacg ccgatatggt     1140
gcccatgcca gccttcgcta taaccccgt gagcgccagc tgtatgcctg ggatgatggc      1200
taccagattg tctacaaatt ggagatgaag aagaaggagg aggaagttta agcagctagc     1260
cttgtgctct tgattcttat gcccagacat ttatattcct gtgagctctc ctgcagttca     1320
tccttcaaaa cgaaggccag tggtggtagc tcatataccc taatttctaa aggacaacca     1380
aattctcaag cccctctgtt ttatgcagaa ctccagatcc tgggtagcat tttagaactg     1440
aacagcaaac aaacacccta aatcttcact cctgccttat gtccacaaag tttagttcca     1500
aactcagagc cctgtccttt ggagagggtc aaccccagac agcaggcgac agcattcttg     1560
ccctcagtat gaccgaaggg agagaactca gagacaaagc tgccctccct cccttccccc     1620
tccagtgtag ggagaatgg ggctttcccc acatcacttt gtatggtaac agtttgcatt      1680
aaaaggaaaa cccaccaaaa aaaaaaaaaa agggcggccg c                         1721
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<210> 128
<211> 406
<212> PRT
<213> Mus musculus

<400> 128

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Met Gly Pro Ser Ala Pro Leu Leu Leu Leu Phe Phe Leu Ser Trp Thr
1               5                   10                  15
Gly Pro Leu Gln Gly Gln Gln His His Leu Val Glu Tyr Met Glu Arg
            20                  25                  30
Arg Leu Ala Ala Leu Glu Glu Arg Leu Ala Gln Cys Gln Asp Gln Ser
        35                  40                  45
Ser Arg His Ala Ala Glu Leu Arg Asp Phe Lys Asn Lys Met Leu Pro
    50                  55                  60
Leu Leu Glu Val Ala Glu Lys Glu Arg Glu Thr Leu Arg Thr Glu Ala
65                  70                  75                  80
Asp Ser Ile Ser Gly Arg Val Asp Arg Leu Glu Arg Glu Val Asp Tyr
                85                  90                  95
Leu Glu Thr Gln Asn Pro Ala Leu Pro Cys Val Glu Leu Asp Glu Lys
            100                 105                 110
Val Thr Gly Gly Pro Gly Ala Lys Gly Lys Gly Arg Arg Asn Glu Lys
        115                 120                 125
Tyr Asp Ile Val Thr Asp Cys Ser Tyr Thr Val Ala Gln Val Arg Ser
    130                 135                 140
Met Lys Ile Leu Lys Arg Phe Gly Gly Ser Val Gly Leu Trp Thr Lys
145                 150                 155                 160
Asp Pro Leu Gly Pro Ala Glu Lys Ile Tyr Val Leu Asp Gly Thr Gln
                165                 170                 175
Asn Asp Thr Ala Phe Val Phe Pro Arg Leu Arg Asp Phe Thr Leu Ala
            180                 185                 190
Met Ala Ala Arg Lys Ala Ser Arg Ile Arg Val Pro Phe Pro Trp Val
        195                 200                 205
Gly Thr Gly Gln Leu Val Tyr Gly Gly Phe Leu Tyr Tyr Ala Arg Arg
    210                 215                 220
Pro Pro Gly Gly Pro Gly Gly Gly Gly Glu Leu Glu Asn Thr Leu Gln
225                 230                 235                 240
Leu Ile Lys Phe His Leu Ala Asn Arg Thr Val Val Asp Ser Ser Val
                245                 250                 255
Phe Pro Ala Glu Ser Leu Ile Pro Pro Tyr Gly Leu Thr Ala Asp Thr
            260                 265                 270
Tyr Ile Asp Leu Ala Ala Asp Glu Glu Gly Leu Trp Ala Val Tyr Ala
        275                 280                 285
Thr Arg Asp Asp Asp Arg His Leu Cys Leu Ala Lys Leu Asp Pro Gln
    290                 295                 300
Thr Leu Asp Thr Glu Gln Gln Trp Asp Thr Pro Cys Pro Arg Glu Asn
305                 310                 315                 320
```

```
Ala Glu Ala Ala Phe Val Ile Cys Gly Thr Leu Tyr Val Val Tyr Asn
                325                 330                 335
Thr Arg Pro Ala Ser Arg Ala Arg Ile Gln Cys Ser Phe Asp Ala Ser
            340                 345                 350
Gly Thr Leu Ala Pro Glu Arg Ala Ala Leu Ser Tyr Phe Pro Arg Arg
        355                 360                 365
Tyr Gly Ala His Ala Ser Leu Arg Tyr Asn Pro Arg Glu Arg Gln Leu
    370                 375                 380
Tyr Ala Trp Asp Asp Gly Tyr Gln Ile Val Tyr Lys Leu Glu Met Lys
385                 390                 395                 400
Lys Lys Glu Glu Glu Val
                405
```

<210> 129
<211> 1721
<212> DNA
<213> Mus musculus

<400> 129
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gtcgacccac gcgtccgact taaggctgcc atggggccca gtgctcctct gctgctcctc      60
ttctttttgt catggacggg acccttcag ggacagcagc accaccttgt ggagtacatg      120
gaacgccgac tagctgcctt agaggaacgg ctggcccaat gccaggatca gagtagtcgg     180
catgctgccg agcttcggga cttcaaaaac aagatgttgc ctctcctgga ggtggcagag     240
aaggagcggg agaccctcag aactgaagca gactccatct caggaagagt ggaccgtctt     300
gaaagggagg tagactatct ggagacacag aacccagctt tgccctgtgt agagctggat     360
gagaaggtga ctggaggtcc tggagccaaa ggcaagggcc gaagaaatga gaaatacgat     420
atagtgacgg actgtagcta cacagtcgct caggtgaggt caatgaagat cctgaagcgg     480
tttggtggtt cagttggcct atggaccaag gatccgctgg ggccagcaga gaagatctac     540
gtgttagacg gcacccagaa cgacacggct tttgtcttcc caaggctgcg tgacttcacc     600
cttgccatgg ctgcccggaa agcttcccga attcgggtgc ccttcccctg ggtaggcacg     660
gggcagctgg tgtacggtgg cttcctttat tatgctcgaa ggcctcctgg aggacctgga     720
gggggtggtg aattggagaa cactctgcag ctgatcaaat ttcacttggc aaaccgaaca     780
gtggtggata gctcagtgtt ccctgcagag agcctgatac ccccctacgg cctgacagca     840
gatacatata tcgacctggc agctgatgag gagggcctgt gggctgtcta tgccactcga     900
gatgatgaca ggcatttgtg tctagccaag ttagacccac agacacttga cacagagcag     960
cagtgggaca caccatgtcc cagagagaac gcagaggctg cgtttgtcat ctgtgggacc    1020
ctgtacgttg tctataacac ccgccctgcc agtagggctc gtattcagtg ttccttcgat    1080
gccagtggta ctctcgcccc tgaaagggca gcactctcct attttccacg ccgatatggt    1140
gcccatgcca gccttcgcta taaccccgt gagcgccagc tgtatgcctg ggatgatggc     1200
taccagattg tctacaaatt ggagatgaag aagaaggagg aggaagttta agcagctagc    1260
cttgtgctct tgattcttat gcccagacat ttatattcct gtgagctctc ctgcagttca    1320
tccttcaaaa cgaaggccag tggtggtagc tcatataccc taatttctaa aggacaacca    1380
aattctcaag cccctctgtt ttatgcagaa ctccagatcc tgggtagcat tttagaactg    1440
aacagcaaac aaacacccta aatcttcact cctgccttat gtccacaaag tttagttcca    1500
aactcagagc cctgtccttt ggagagggtc aaccccagac agcaggcgac agcattcttg    1560
ccctcagtat gaccgaaggg agagaactca gagacaaagc tgccctccct cccttccccc    1620
tccagtgtag gggagaatgg ggctttcccc acatcacttt gtatggtaac agtttgcatt    1680
aaaaggaaaa cccaccaaaa aaaaaaaaaa agggcggccg c                         1721
```

<210> 130
<211> 406
<212> PRT
<213> Mus musculus

<400> 130
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Met Gly Pro Ser Ala Pro Leu Leu Leu Leu Phe Phe Leu Ser Trp Thr
1               5                   10                  15
Gly Pro Leu Gln Gly Gln Gln His His Leu Val Glu Tyr Met Glu Arg
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```
                20                       25                       30
Arg Leu Ala Ala Leu Glu Glu Arg Leu Ala Gln Cys Gln Asp Gln Ser
            35                       40                       45
Ser Arg His Ala Ala Glu Leu Arg Asp Phe Lys Asn Lys Met Leu Pro
    50                       55                       60
Leu Leu Glu Val Ala Glu Lys Glu Arg Glu Thr Leu Arg Thr Glu Ala
65                       70                       75                       80
Asp Ser Ile Ser Gly Arg Val Asp Arg Leu Glu Arg Glu Val Asp Tyr
                85                       90                       95
Leu Glu Thr Gln Asn Pro Ala Leu Pro Cys Val Glu Leu Asp Glu Lys
            100                      105                      110
Val Thr Gly Gly Pro Gly Ala Lys Gly Lys Gly Arg Arg Asn Glu Lys
        115                      120                      125
Tyr Asp Met Val Thr Asp Cys Ser Tyr Thr Val Ala Gln Val Arg Ser
    130                      135                      140
Met Lys Ile Leu Lys Arg Phe Gly Gly Ser Val Gly Leu Trp Thr Lys
145                      150                      155                      160
Asp Pro Leu Gly Pro Ala Glu Lys Ile Tyr Ala Leu Asp Gly Thr Gln
                165                      170                      175
Asn Asp Thr Ala Phe Val Phe Pro Arg Leu Arg Asp Phe Thr Leu Ala
            180                      185                      190
Met Ala Ala Arg Lys Ala Ser Arg Ile Arg Val Pro Phe Pro Trp Val
        195                      200                      205
Gly Thr Gly Gln Leu Val Tyr Gly Gly Phe Leu Tyr Tyr Ala Arg Arg
    210                      215                      220
Pro Pro Gly Gly Pro Gly Gly Gly Gly Glu Leu Glu Asn Thr Leu Gln
225                      230                      235                      240
Leu Ile Lys Phe His Leu Ala Asn Arg Thr Val Val Asp Ser Ser Val
                245                      250                      255
Phe Pro Ala Glu Ser Leu Ile Pro Pro Tyr Gly Leu Thr Ala Asp Thr
            260                      265                      270
Tyr Ile Asp Leu Ala Ala Asp Glu Glu Gly Leu Trp Ala Val Tyr Ala
        275                      280                      285
Thr Arg Asp Asp Asp Arg His Leu Cys Leu Ala Lys Leu Asp Pro Gln
    290                      295                      300
Thr Leu Asp Thr Glu Gln Gln Trp Asp Thr Pro Cys Pro Arg Glu Asn
305                      310                      315                      320
Ala Glu Ala Ala Phe Val Ile Cys Gly Thr Leu Tyr Val Val Tyr Asn
                325                      330                      335
Thr Arg Pro Ala Ser Arg Ala Arg Ile Gln Cys Ser Phe Asp Ala Ser
            340                      345                      350
Gly Thr Leu Ala Pro Glu Arg Ala Ala Leu Ser Tyr Phe Pro Arg Arg
        355                      360                      365
Tyr Gly Ala His Ala Ser Leu Arg Tyr Asn Pro Arg Glu Arg Gln Leu
    370                      375                      380
Tyr Ala Trp Asp Asp Gly Tyr Gln Ile Val Tyr Lys Leu Glu Met Lys
385                      390                      395                      400
Lys Lys Glu Glu Glu Val
                405
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<210> 131
<211> 1721
<212> DNA
<213> Mus musculus

<400> 131

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gtcgacccac gcgtccgact taaggctgcc atggggccca gtgctcctct gctgctcctc      60
ttctttttgt catggacggg accccttcag ggacagcagc accaccttgt ggagtacatg     120
```

gaacgccgac tagctgcctt agaggaacgg ctggcccaat gccaggatca gagtagtcgg 180
catgctgccg agcttcggga cttcaaaaac aagatgttgc ctctcctgga ggtggcagag 240
aaggagcggg agaccctcag aactgaagca gactccatct caggaagagt ggaccgtctt 300
gaaagggagg tagactatct ggagacacag aacccagctt tgccctgtgt agagctggat 360
gagaaggtga ctggaggtcc tggagccaaa ggcaagggcc gaagaaatga gaaatacgat 420
atggtgacgg actgtagcta cacagtcgct caggtgaggt caatgaagat cctgaagcgg 480
tttggtggtt cagttggcct atggaccaag gatccgctgg ggccagcaga gaagatctac 540
gcgttagacg gcacccagaa cgacacggct tttgtcttcc caaggctgcg tgacttcacc 600
cttgccatgg ctgcccggaa agcttcccga attcgggtgc ccttcccctg ggtaggcacg 660
gggcagctgg tgtacggtgg cttcctttat tatgctcgaa ggcctcctgg aggacctgga 720
gggggtggtg aattggagaa cactctgcag ctgatcaaat ttcacttggc aaaccgaaca 780
gtggtggata gctcagtgtt ccctgcagag agcctgatac ccccctacgg cctgacagca 840
gatacatata tcgacctggc agctgatgag gagggcctgt gggctgtcta tgccactcga 900
gatgatgaca ggcatttgtg tctagccaag ttagacccac agacacttga cacagagcag 960
cagtgggaca caccatgtcc cagagagaac gcagaggctg cgtttgtcat ctgtgggacc 1020
ctgtacgttg tctataacac ccgccctgcc agtagggctc gtattcagtg ttccttcgat 1080
gccagtggta ctctcgcccc tgaaagggca gcactctcct atttccacg ccgatatggt 1140
gcccatgcca gccttcgcta taaccccgt gagcgccagc tgtatgcctg ggatgatggc 1200
taccagattg tctacaaatt ggagatgaag aagaaggagg aggaagttta agcagctagc 1260
cttgtgctct tgattcttat gcccagacat ttatattcct gtgagctctc ctgcagttca 1320
tccttcaaaa cgaaggccag tggtggtagc tcatataccc taatttctaa aggacaacca 1380
aattctcaag cccctctgtt ttatgcagaa ctccagatcc tgggtagcat tttagaactg 1440
aacagcaaac aaacacccta aatcttcact cctgccttat gtccacaaag tttagttcca 1500
aactcagagc cctgtccttt ggagagggtc aaccccagac agcaggcgac agcattcttg 1560
ccctcagtat gaccgaaggg agagaactca gagacaaagc tgccctccct cccttccccc 1620
tccagtgtag ggagaatggg ggctttcccc acatcacttt gtatggtaac agtttgcatt 1680
aaaaggaaaa cccaccaaaa aaaaaaaaaa agggcggccg c 1721

<210> 132
<211> 406
<212> PRT
<213> Mus musculus

<400> 132
Met Gly Pro Ser Ala Pro Leu Leu Leu Leu Phe Phe Leu Ser Trp Thr
1 5 10 15
Gly Pro Leu Gln Gly Gln Gln His His Leu Val Glu Tyr Met Glu Arg
20 25 30
Arg Leu Ala Ala Leu Glu Glu Arg Leu Ala Gln Cys Gln Asp Gln Ser
35 40 45
Ser Arg His Ala Ala Glu Leu Arg Asp Phe Lys Asn Lys Met Leu Pro
50 55 60
Leu Leu Glu Val Ala Glu Lys Glu Arg Glu Thr Leu Arg Thr Glu Ala
65 70 75 80
Asp Ser Ile Ser Gly Arg Val Asp Arg Leu Glu Arg Glu Val Asp Tyr
85 90 95
Leu Glu Thr Gln Asn Pro Ala Leu Pro Cys Val Glu Leu Asp Glu Lys
100 105 110
Val Thr Gly Gly Pro Gly Ala Lys Gly Lys Gly Arg Arg Asn Glu Lys
115 120 125
Tyr Asp Met Val Thr Asp Cys Ser Tyr Thr Val Ala Gln Val Arg Ser
130 135 140
Met Lys Ile Leu Lys Arg Phe Gly Gly Ser Val Gly Leu Trp Thr Lys
145 150 155 160
Asp Pro Leu Gly Pro Ala Glu Lys Ile Tyr Val Leu Asp Gly Thr Gln
165 170 175
Asn Asp Thr Ala Phe Val Phe Pro Arg Leu Arg Asp Phe Thr Leu Val
180 185 190

```
Met Ala Ala Arg Lys Ala Ser Arg Ile Arg Val Pro Phe Pro Trp Val
        195                 200                 205
Gly Thr Gly Gln Leu Val Tyr Gly Gly Phe Leu Tyr Tyr Ala Arg Arg
    210                 215                 220
Pro Pro Gly Gly Pro Gly Gly Gly Gly Glu Leu Glu Asn Thr Leu Gln
225                 230                 235                     240
Leu Ile Lys Phe His Leu Ala Asn Arg Thr Val Val Asp Ser Ser Val
                245                 250                 255
Phe Pro Ala Glu Ser Leu Ile Pro Pro Tyr Gly Leu Thr Ala Asp Thr
            260                 265                 270
Tyr Ile Asp Leu Ala Ala Asp Glu Glu Gly Leu Trp Ala Val Tyr Ala
        275                 280                 285
Thr Arg Asp Asp Asp Arg His Leu Cys Leu Ala Lys Leu Asp Pro Gln
    290                 295                 300
Thr Leu Asp Thr Glu Gln Gln Trp Asp Thr Pro Cys Pro Arg Glu Asn
305                 310                 315                     320
Ala Glu Ala Ala Phe Val Ile Cys Gly Thr Leu Tyr Val Val Tyr Asn
                325                 330                 335
Thr Arg Pro Ala Ser Arg Ala Arg Ile Gln Cys Ser Phe Asp Ala Ser
            340                 345                 350
Gly Thr Leu Ala Pro Glu Arg Ala Ala Leu Ser Tyr Phe Pro Arg Arg
        355                 360                 365
Tyr Gly Ala His Ala Ser Leu Arg Tyr Asn Pro Arg Glu Arg Gln Leu
    370                 375                 380
Tyr Ala Trp Asp Asp Gly Tyr Gln Ile Val Tyr Lys Leu Glu Met Lys
385                 390                 395                     400
Lys Lys Glu Glu Glu Val
                405
```

<210> 133
<211> 1721
<212> DNA
<213> Mus musculus

<400> 133

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gtcgacccac gcgtccgact taaggctgcc atggggccca gtgctcctct gctgctcctc      60
ttctttttgt catggacggg acccccttcag ggacagcagc accaccttgt ggagtacatg    120
gaacgccgac tagctgcctt agaggaacgg ctggcccaat gccaggatca gagtagtcgg     180
catgctgccg agcttcggga cttcaaaaac aagatgttgc ctctcctgga ggtggcagag     240
aaggagcggg agaccctcag aactgaagca gactccatct caggaagagt ggaccgtctt     300
gaaagggagg tagactatct ggagacacag aacccagctt tgccctgtgt agagctggat     360
gagaaggtga ctggaggtcc tggagccaaa ggcaagggcc gaagaaatga gaaatacgat     420
atggtgacgg actgtagcta cacagtcgct caggtgaggt caatgaagat cctgaagcgg     480
tttggtggtt cagttggcct atggaccaag gatccgctgg ggccagcaga gaagatctac     540
gtgttagacg gcacccagaa cgacacggct tttgtcttcc caaggctgcg tgacttcacc     600
cttgtcatgg ctgcccggaa agcttcccga attcgggtgc ccttcccctg ggtaggcacg     660
gggcagctgg tgtacggtgg cttcctttat tatgctcgaa ggcctcctgg aggacctgga     720
gggggtggtg aattggagaa cactctgcag ctgatcaaat ttcacttggc aaaccgaaca     780
gtggtggata gctcagtgtt ccctgcagag agcctgatac ccccctacgg cctgacagca     840
gatacatata tcgacctggc agctgatgag gagggcctgt gggctgtcta tgccactcga     900
gatgatgaca ggcatttgtg tctagccaag ttagacccac agacacttga cacagagcag     960
cagtgggaca caccatgtcc cagagagaac gcagaggctg cgtttgtcat ctgtgggacc    1020
ctgtacgttg tctataacac ccgccctgcc agtagggctc gtattcagtg ttccttcgat    1080
gccagtggta ctctcgcccc tgaaagggca gcactctcct attttccacg ccgatatggt    1140
gcccatgcca gccttcgcta taaccccccgt gagcgccagc tgtatgcctg ggatgatggc  1200
taccagattg tctacaaatt ggagatgaag aagaaggagg aggaagttta agcagctagc    1260
cttgtgctct tgattcttat gcccagacat ttatattcct gtgagctctc ctgcagttca    1320
tccttcaaaa cgaaggccag tggtggtagc tcatataccc taatttctaa aggacaacca    1380
```

```
aattctcaag cccctctgtt ttatgcagaa ctccagatcc tgggtagcat tttagaactg    1440
aacagcaaac aaacacccta aatcttcact cctgccttat gtccacaaag tttagttcca    1500
aactcagagc cctgtccttt ggagagggtc aaccccagac agcaggcgac agcattcttg    1560
ccctcagtat gaccgaaggg agagaactca gagacaaagc tgccctccct cccttccccc    1620
tccagtgtag gggagaatgg ggctttcccc acatcacttt gtatggtaac agtttgcatt    1680
aaaaggaaaa cccaccaaaa aaaaaaaaaa agggcggccg c                        1721
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<210> 134
<211> 370
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (13)
<223> Xaa=unknown amino acid

<400> 134

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Met Ile Ser Leu Pro Gly Pro Leu Val Thr Asn Leu Xaa Arg Phe Leu
1               5                   10                  15
Phe Leu Gly Leu Ser Ala Leu Ala Pro Pro Ser Arg Ala Gln Leu Gln
            20                  25                  30
Leu His Leu Pro Ala Asn Arg Leu Gln Ala Val Glu Glu Gly Glu Ser
        35                  40                  45
Gly Ala Ser Ala Trp Tyr Thr Leu His Arg Glu Ala Ser Ser Ser Gln
    50                  55                  60
Pro Trp Glu Val Pro Phe Val Met Trp Phe Phe Lys Gln Lys Glu Lys
65                  70                  75                  80
Glu Asp Gln Val Leu Ser Tyr Ile Asn Gly Val Thr Thr Ser Lys Pro
                85                  90                  95
Gly Val Ser Leu Val Tyr Ser Met Pro Ser Arg Asn Leu Ser Leu Arg
            100                 105                 110
Val Glu Gly Leu Gln Glu Lys Asp Ser Gly Pro Tyr Ser Cys Ser Val
        115                 120                 125
Asn Val Gln Asp Lys Gln Gly Lys Ser Arg Gly His Ser Ile Lys Thr
    130                 135                 140
Leu Glu Leu Asn Val Leu Val Pro Pro Ala Pro Pro Ser Cys Arg Leu
145                 150                 155                 160
Gln Gly Val Pro His Val Gly Ala Asn Val Thr Leu Ser Cys Gln Ser
                165                 170                 175
Pro Arg Ser Lys Pro Ala Val Gln Tyr Gln Trp Asp Arg Gln Leu Pro
            180                 185                 190
Ser Phe Gln Thr Phe Phe Ala Pro Ala Leu Asp Val Ile Arg Gly Ser
        195                 200                 205
Leu Ser Leu Thr Asn Leu Ser Ser Ser Met Ala Gly Val Tyr Val Cys
    210                 215                 220
Lys Ala His Asn Glu Val Gly Thr Ala Gln Cys Asn Val Thr Leu Glu
225                 230                 235                 240
Val Ser Thr Gly Pro Gly Ala Ala Val Val Ala Glu Ala Val Val Gly
                245                 250                 255
Thr Leu Val Gly Leu Gly Leu Leu Ala Gly Leu Val Leu Leu Tyr His
            260                 265                 270
Arg Arg Gly Lys Ala Leu Glu Glu Pro Ala Asn Asp Ile Lys Glu Asp
        275                 280                 285
Ala Ile Ala Pro Arg Thr Leu Pro Trp Pro Lys Ser Ser Asp Thr Ile
    290                 295                 300
Ser Lys Asn Gly Thr Leu Ser Ser Val Thr Ser Ala Arg Ala Leu Arg
305                 310                 315                 320
```

```
Pro Pro His Gly Pro Pro Arg Pro Gly Ala Leu Thr Pro Thr Pro Ser
                325                 330                 335
Leu Ser Ser Gln Ala Leu Pro Ser Pro Arg His Ala His Asp Arg Trp
            340                 345                 350
Gly Pro Pro Ser Thr Asn Ile Pro His Pro Trp Trp Gly Phe Phe Leu
        355                 360                 365
Trp Leu
    370
```

<210> 135
<211> 1869
<212> DNA
<213> Homo sapiens

<220>
<221> modified_base
<222> all "n" positions
<223> n=a, c, g, or t

<400> 135

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gcgcacgctc cggccgtcgc gcagcctcgg cacctgcagg tccgtgcgtc ccgcggctgg    120
cgcccctgac tccgtcccgg ccagggaggg ccatgatttc cctcccgggg cccctggtga    180
ccaacttgnt gcggtttttg ttcctggggc tgagtgccct cgcgcccccc tcgcgggccc    240
agctgcaact gcacttgccc gccaaccggt tgcaggcggt ggaggagggg gaaagtggtg    300
cttcagcatg gtacaccttg cacagggagg cgtcttcatc ccagccatgg gaggtgccct    360
ttgtgatgtg gttcttcaaa cagaaagaaa aggaggatca ggtgttgtcc tacatcaatg    420
gggtcacaac aagcaaacct ggagtatcct tggtctactc catgccctcc cggaacctgt    480
ccctgcgggt ggagggtctc caggagaaag actctggccc ctacagctgc tccgtgaatg    540
tgcaagacaa acaaggcaaa tctaggggcc acagcatcaa aaccttagaa ctcaatgtac    600
tggttcctcc agctcctcca tcctgccgtc tccagggtgt gccccatgtg gggcaaacg     660
tgaccctgag ctgccagtct ccaaggagta agcccgctgt ccaataccag tgggatcggc    720
agcttccatc cttccagact ttctttgcac cagcattaga tgtcatccgt gggtctttaa    780
gcctcaccaa cctttcgtct tccatggctg gagtctatgt ctgcaaggcc cacaatgagg    840
tgggcactgc ccaatgtaat gtgacgctgg aagtgagcac agggcctgga gctgcagtgg    900
ttgctgaagc tgttgtgggt accctggttg gactggggtt gctggctggg ctggtcctct    960
tgtaccaccg ccggggcaag gccctggagg agccagccaa tgatatcaag gaggatgcca   1020
ttgctccccg gaccctgccc tggcccaaga gctcagacac aatctccaag aatgggaccc   1080
tttcctctgt cacctccgca cgagccctcc ggccacccca tggccctccc aggcctggtg   1140
cattgacccc cacgcccagt ctatccagcc aggccctgcc ctcaccaaga catgcccacg   1200
acagatgggg cccaccctca accaatatcc cccatccctg gtggggtttt ttcctttggc   1260
tttgagccgc atgggtgctg ngcctgtgat ggngcctgcc cagagtcaag ctggctctct   1320
ggtatgatga ccccaccact cattggctaa aggatttggg gtctctcctt cctataaggg   1380
tcacctctag cacagaggcc tgagtcatgg gaaagagtca cactcctgac ccttagtact   1440
ctgcccccac ctctctttac tgtgggaaaa ccatctcagt aagacctaag tgtccaggag   1500
acagaaggag aagaggaagt ggatctggaa ttgggaggag cctccaccca cccctgactc   1560
ctccttatga agccagctgc tgaaattagc tactcaccaa gagtgagggg cagagacttc   1620
cagtcactga gtctcccagg ccccttgat ctgtacccca cccctatcta acaccaccct    1680
tggctcccac tccagctccc tgtattgata taacctgtca ggctggcttg gttaggtttt   1740
actggggcag aggataggga atctcttatt aaaactaaca tgaaatatgt gttgttttca   1800
tttgcaaatt taaataaaga tacataatgt ttgtatgaga taagaaaaaa aaaaaaaaag   1860
ggcggccgc                                                           1869
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<210> 136
<211> 370
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (13)
<223> Xaa=unknown amino acid

<400> 136
Met Ile Ser Leu Pro Gly Pro Leu Val Thr Asn Leu Xaa Arg Phe Leu
1 5 10 15
Phe Leu Gly Leu Ser Ala Leu Ala Pro Pro Ser Arg Ala Gln Leu Gln
20 25 30
Leu His Leu Pro Ala Asn Arg Leu Gln Ala Val Glu Glu Gly Glu Ser
35 40 45
Gly Ala Ser Ala Trp Tyr Thr Leu His Arg Glu Val Ser Ser Ser Gln
50 55 60
Pro Trp Glu Val Pro Phe Val Met Trp Phe Phe Lys Gln Lys Glu Lys
65 70 75 80
Glu Asp Gln Val Leu Ser Tyr Ile Asn Gly Val Thr Thr Ser Lys Pro
85 90 95
Gly Val Ser Leu Ala Tyr Ser Met Pro Ser Arg Asn Leu Ser Leu Arg
100 105 110
Val Glu Gly Leu Gln Glu Lys Asp Ser Gly Pro Tyr Ser Cys Ser Val
115 120 125
Asn Val Gln Asp Lys Gln Gly Lys Ser Arg Gly His Ser Ile Lys Thr
130 135 140
Leu Glu Leu Asn Val Leu Val Pro Pro Ala Pro Pro Ser Cys Arg Leu
145 150 155 160
Gln Gly Val Pro His Val Gly Ala Asn Val Thr Leu Ser Cys Gln Ser
165 170 175
Pro Arg Ser Lys Pro Ala Val Gln Tyr Gln Trp Asp Arg Gln Leu Pro
180 185 190
Ser Phe Gln Thr Phe Phe Ala Pro Ala Leu Asp Val Ile Arg Gly Ser
195 200 205
Leu Ser Leu Thr Asn Leu Ser Ser Ser Met Ala Gly Val Tyr Val Cys
210 215 220
Lys Ala His Asn Glu Val Gly Thr Ala Gln Cys Asn Val Thr Leu Glu
225 230 235 240
Val Ser Thr Gly Pro Gly Ala Ala Val Val Ala Glu Ala Val Val Gly
245 250 255
Thr Leu Val Gly Leu Gly Leu Leu Ala Gly Leu Val Leu Leu Tyr His
260 265 270
Arg Arg Gly Lys Ala Leu Glu Glu Pro Ala Asn Asp Ile Lys Glu Asp
275 280 285
Ala Ile Ala Pro Arg Thr Leu Pro Trp Pro Lys Ser Ser Asp Thr Ile
290 295 300
Ser Lys Asn Gly Thr Leu Ser Ser Val Thr Ser Ala Arg Ala Leu Arg
305 310 315 320
Pro Pro His Gly Pro Pro Arg Pro Gly Ala Leu Thr Pro Thr Pro Ser
325 330 335
Leu Ser Ser Gln Ala Leu Pro Ser Pro Arg His Ala His Asp Arg Trp
340 345 350
Gly Pro Pro Ser Thr Asn Ile Pro His Pro Trp Trp Gly Phe Phe Leu
355 360 365
Trp Leu
370

<210> 137
<211> 1869

<212> DNA
<213> Homo sapiens

<220>
<221> modified_base
<222> all "n" positions
<223> n=a, c, g, or t

<400> 137
gtcgacccac gcgtncntcc agcgtncgga gccgccctgg gtgtcagcgg ctcggctccc 60
gcgcacgctc cggccgtcgc gcagcctcgg cacctgcagg tccgtgcgtc ccgcggctgg 120
cgcccctgac tccgtcccgg ccagggaggg ccatgatttc cctcccgggg cccctggtga 180
ccaacttgnt gcggtttttg ttcctggggc tgagtgccct cgcgcccccc tcgcgggccc 240
agctgcaact gcacttgccc gccaaccggt tgcaggcggt ggaggagggg gaaagtggtg 300
cttcagcatg gtacaccttg cacagggagg tgtcttcatc ccagccatgg gaggtgccct 360
ttgtgatgtg gttcttcaaa cagaaagaaa aggaggatca ggtgttgtcc tacatcaatg 420
gggtcacaac aagcaaacct ggagtatcct tggcctactc catgccctcc cggaacctgt 480
ccctgcgggt ggagggtctc caggagaaag actctggccc ctacagctgc tccgtgaatg 540
tgcaagacaa acaaggcaaa tctaggggcc acagcatcaa aaccttagaa ctcaatgtac 600
tggttcctcc agctcctcca tcctgccgtc tccagggtgt gccccatgtg gggggcaaacg 660
tgaccctgag ctgccagtct ccaaggagta agcccgctgt ccaataccag tgggatcggc 720
agcttccatc cttccagact ttctttgcac cagcattaga tgtcatccgt gggtctttaa 780
gcctcaccaa cctttcgtct tccatggctg gagtctatgt ctgcaaggcc cacaatgagg 840
tgggcactgc ccaatgtaat gtgacgctgg aagtgagcac agggcctgga gctgcagtgg 900
ttgctgaagc tgttgtgggt accctggttg gactggggtt gctggctggg ctggtcctct 960
tgtaccaccg ccggggcaag gccctggagg agccagccaa tgatatcaag gaggatgcca 1020
ttgctccccg gaccctgccc tggcccaaga gctcagacac aatctccaag aatgggaccc 1080
tttcctctgt cacctccgca cgagccctcc ggccacccca tggccctccc aggcctggtg 1140
cattgacccc cacgcccagt ctatccagcc aggccctgcc ctcaccaaga catgcccacg 1200
acagatgggg cccaccctca accaatatcc cccatccctg gtggggtttt ttcctttggc 1260
tttgagccgc atgggtgctg ngcctgtgat ggngcctgcc cagagtcaag ctggctctct 1320
ggtatgatga ccccaccact cattggctaa aggatttggg gtctctcctt cctataaggg 1380
tcacctctag cacagaggcc tgagtcatgg gaaagagtca cactcctgac ccttagtact 1440
ctgcccccac ctctctttac tgtgggaaaa ccatctcagt aagacctaag tgtccaggag 1500
acagaaggag aagaggaagt ggatctggaa ttgggaggag cctccaccca cccctgactc 1560
ctccttatga agccagctgc tgaaattagc tactcaccaa gagtgagggg cagagacttc 1620
cagtcactga gtctcccagg ccccccttgat ctgtacccca cccctatcta acaccaccct 1680
tggctcccac tccagctccc tgtattgata taacctgtca ggctggcttg gttaggtttt 1740
actggggcag aggataggga atctcttatt aaaactaaca tgaaatatgt gttgttttca 1800
tttgcaaatt taaataaaga tacataatgt ttgtatgaga taagaaaaaa aaaaaaaaag 1860
ggcggccgc 1869

<210> 138
<211> 370
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (13)
<223> Xaa=unknown amino acid

<400> 138
Met Ile Ser Leu Pro Gly Pro Leu Val Thr Asn Leu Xaa Arg Phe Leu
1 5 10 15
Phe Leu Gly Leu Ser Ala Leu Ala Pro Pro Ser Arg Ala Gln Leu Gln
20 25 30

```
Leu His Leu Pro Ala Asn Arg Leu Gln Ala Val Glu Glu Gly Glu Ser
        35                  40                  45
Gly Ala Ser Ala Trp Tyr Thr Leu His Arg Glu Val Ser Ser Ser Gln
    50                  55                  60
Pro Trp Glu Val Pro Phe Val Met Trp Phe Phe Lys Gln Lys Glu Lys
65                  70                  75                  80
Glu Asp Gln Val Leu Ser Tyr Ile Asn Gly Val Thr Thr Ser Lys Pro
                85                  90                  95
Gly Val Ser Leu Val Tyr Ser Met Pro Ser Arg Asn Leu Ser Leu Arg
            100                 105                 110
Val Glu Gly Leu Gln Glu Lys Asp Ser Gly Pro Tyr Ser Cys Ser Val
        115                 120                 125
Asn Val Gln Asp Lys Gln Gly Lys Ser Arg Gly His Ser Ile Lys Thr
    130                 135                 140
Leu Glu Leu Asn Val Leu Val Pro Pro Ala Pro Pro Ser Cys Arg Ile
145                 150                 155                 160
Gln Gly Val Pro His Val Gly Ala Asn Val Thr Leu Ser Cys Gln Ser
                165                 170                 175
Pro Arg Ser Lys Pro Ala Val Gln Tyr Gln Trp Asp Arg Gln Leu Pro
            180                 185                 190
Ser Phe Gln Thr Phe Phe Ala Pro Ala Leu Asp Val Ile Arg Gly Ser
        195                 200                 205
Leu Ser Leu Thr Asn Leu Ser Ser Ser Met Ala Gly Val Tyr Val Cys
    210                 215                 220
Lys Ala His Asn Glu Val Gly Thr Ala Gln Cys Asn Val Thr Leu Glu
225                 230                 235                 240
Val Ser Thr Gly Pro Gly Ala Ala Val Val Ala Glu Ala Val Val Gly
                245                 250                 255
Thr Leu Val Gly Leu Gly Leu Leu Ala Gly Leu Val Leu Leu Tyr His
            260                 265                 270
Arg Arg Gly Lys Ala Leu Glu Glu Pro Ala Asn Asp Ile Lys Glu Asp
        275                 280                 285
Ala Ile Ala Pro Arg Thr Leu Pro Trp Pro Lys Ser Ser Asp Thr Ile
    290                 295                 300
Ser Lys Asn Gly Thr Leu Ser Ser Val Thr Ser Ala Arg Ala Leu Arg
305                 310                 315                 320
Pro Pro His Gly Pro Pro Arg Pro Gly Ala Leu Thr Pro Thr Pro Ser
                325                 330                 335
Leu Ser Ser Gln Ala Leu Pro Ser Pro Arg His Ala His Asp Arg Trp
            340                 345                 350
Gly Pro Pro Ser Thr Asn Ile Pro His Pro Trp Trp Gly Phe Phe Leu
        355                 360                 365
Trp Leu
    370

<210> 139
<211> 1869
<212> DNA
<213> Homo sapiens

<220>
<221> modified_base
<222> all "n" positions
<223> n=a, c, g, or t

<400> 139
gtcgacccac gcgtncntcc agcgtncgga gccgccctgg gtgtcagcgg ctcggctccc      60
gcgcacgctc cggccgtcgc gcagcctcgg cacctgcagg tccgtgcgtc ccgcggctgg     120
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```
cgcccctgac tccgtcccgg ccagggaggg ccatgatttc cctcccgggg cccctggtga   180
ccaacttgnt gcggtttttg ttcctggggc tgagtgccct cgcgcccccc tcgcgggccc   240
agctgcaact gcacttgccc gccaaccggt tgcaggcggt ggaggagggg gaaagtggtg   300
cttcagcatg gtacaccttg cacagggagg tgtcttcatc ccagccatgg gaggtgccct   360
ttgtgatgtg gttcttcaaa cagaaagaaa aggaggatca ggtgttgtcc tacatcaatg   420
gggtcacaac aagcaaacct ggagtatcct tggtctactc catgccctcc cggaacctgt   480
ccctgcgggt ggagggtctc caggagaaag actctggccc ctacagctgc tccgtgaatg   540
tgcaagacaa acaaggcaaa tctaggggcc acagcatcaa aaccttagaa ctcaatgtac   600
tggttcctcc agctcctcca tcctgccgta tccagggtgt gccccatgtg gggcaaacg   660
tgaccctgag ctgccagtct ccaaggagta agcccgctgt ccaataccag tgggatcggc   720
agcttccatc cttccagact ttctttgcac cagcattaga tgtcatccgt gggtctttaa   780
gcctcaccaa cctttcgtct tccatggctg gagtctatgt ctgcaaggcc cacaatgagg   840
tgggcactgc ccaatgtaat gtgacgctgg aagtgagcac agggcctgga gctgcagtgg   900
ttgctgaagc tgttgtgggt accctggttg gactggggtt gctggctggg ctggtcctct   960
tgtaccaccg ccggggcaag gccctggagg agccagccaa tgatatcaag gaggatgcca   1020
ttgctccccg gaccctgccc tggcccaaga gctcagacac aatctccaag aatgggaccc   1080
tttcctctgt cacctccgca cgagccctcc ggccacccca tggccctccc aggcctggtg   1140
cattgacccc cacgcccagt ctatccagcc aggccctgcc ctcaccaaga catgcccacg   1200
acagatgggg cccaccctca accaatatcc cccatccctg gtggggtttt ttcctttggc   1260
tttgagccgc atgggtgctg ngcctgtgat ggngcctgcc cagagtcaag ctggctctct   1320
ggtatgatga ccccaccact cattggctaa aggatttggg gtctctcctt cctataaggg   1380
tcacctctag cacagaggcc tgagtcatgg gaaagagtca cactcctgac ccttagtact   1440
ctgcccccac ctctctttac tgtgggaaaa ccatctcagt aagacctaag tgtccaggag   1500
acagaaggag aagaggaagt ggatctggaa ttgggaggag cctccaccca cccctgactc   1560
ctccttatga agccagctgc tgaaattagc tactcaccaa gagtgagggg cagagacttc   1620
cagtcactga gtctcccagg ccccccttgat ctgtacccca cccctatcta acaccaccct   1680
tggctcccac tccagctccc tgtattgata taacctgtca ggctggcttg gttaggtttt   1740
actggggcag aggataggga atctcttatt aaaactaaca tgaaatatgt gttgttttca   1800
tttgcaaatt taaataaaga tacataatgt ttgtatgaga taagaaaaaa aaaaaaaaag   1860
ggcggccgc                                                          1869
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<210> 140
<211> 370
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (13)
<223> Xaa=unknown amino acid

<400> 140

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Met Ile Ser Leu Pro Gly Pro Leu Val Thr Asn Leu Xaa Arg Phe Leu
 1               5                  10                  15
Phe Leu Gly Leu Ser Ala Leu Ala Pro Pro Ser Arg Ala Gln Leu Gln
            20                  25                  30
Leu His Leu Pro Ala Asn Arg Leu Gln Ala Val Glu Glu Gly Glu Ser
        35                  40                  45
Gly Ala Ser Ala Trp Tyr Thr Leu His Arg Glu Val Ser Ser Ser Gln
    50                  55                  60
Pro Trp Glu Val Pro Phe Val Met Trp Phe Phe Lys Gln Lys Glu Lys
65                  70                  75                  80
Glu Asp Gln Val Leu Ser Tyr Ile Asn Gly Val Thr Thr Ser Lys Pro
                85                  90                  95
Gly Val Ser Leu Val Tyr Ser Met Pro Ser Arg Asn Leu Ser Leu Arg
            100                 105                 110
Val Glu Gly Leu Gln Glu Lys Asp Ser Gly Pro Tyr Ser Cys Ser Val
        115                 120                 125
```

```
Asn Val Gln Asp Lys Gln Gly Lys Ser Arg Gly His Ser Ile Lys Thr
    130                 135                 140
Leu Glu Leu Asn Val Leu Val Pro Pro Ala Pro Pro Ser Cys Arg Leu
145                 150                 155                 160
Gln Gly Val Pro His Val Gly Ala Asn Val Thr Leu Ser Cys Gln Ser
                165                 170                 175
Pro Arg Ser Lys Pro Val Val Gln Tyr Gln Trp Asp Arg Gln Leu Pro
            180                 185                 190
Ser Phe Gln Thr Phe Phe Ala Pro Ala Leu Asp Val Ile Arg Gly Ser
        195                 200                 205
Leu Ser Leu Thr Asn Leu Ser Ser Ser Met Ala Gly Val Tyr Val Cys
    210                 215                 220
Lys Ala His Asn Glu Val Gly Thr Ala Gln Cys Asn Val Thr Leu Glu
225                 230                 235                 240
Val Ser Thr Gly Pro Gly Ala Ala Val Val Ala Glu Ala Val Val Gly
                245                 250                 255
Thr Leu Val Gly Leu Gly Leu Leu Ala Gly Leu Val Leu Leu Tyr His
            260                 265                 270
Arg Arg Gly Lys Ala Leu Glu Glu Pro Ala Asn Asp Ile Lys Glu Asp
        275                 280                 285
Ala Ile Ala Pro Arg Thr Leu Pro Trp Pro Lys Ser Ser Asp Thr Ile
    290                 295                 300
Ser Lys Asn Gly Thr Leu Ser Ser Val Thr Ser Ala Arg Ala Leu Arg
305                 310                 315                 320
Pro Pro His Gly Pro Pro Arg Pro Gly Ala Leu Thr Pro Thr Pro Ser
                325                 330                 335
Leu Ser Ser Gln Ala Leu Pro Ser Pro Arg His Ala His Asp Arg Trp
            340                 345                 350
Gly Pro Pro Ser Thr Asn Ile Pro His Pro Trp Trp Gly Phe Phe Leu
        355                 360                 365
Trp Leu
    370

<210> 141
<211> 1869
<212> DNA
<213> Homo sapiens

<220>
<221> modified_base
<222> all "n" positions
<223> n=a, c, g, or t

<400> 141
gtcgacccac gcgtncntcc agcgtncgga gccgccctgg gtgtcagcgg ctcggctccc    60
gcgcacgctc cggccgtcgc gcagcctcgg cacctgcagg tccgtgcgtc ccgcggctgg   120
cgcccctgac tccgtcccgg ccagggaggg ccatgatttc cctcccgggg cccctggtga   180
ccaacttgnt gcggtttttg ttcctggggc tgagtgccct cgcgcccccc tcgcgggccc   240
agctgcaact gcacttgccc gccaaccggt tgcaggcggt ggaggagggg gaaagtggtg   300
cttcagcatg gtacaccttg cacagggagg tgtcttcatc ccagccatgg gaggtgccct   360
ttgtgatgtg gttcttcaaa cagaaagaaa aggaggatca ggtgttgtcc tacatcaatg   420
gggtcacaac aagcaaacct ggagtatcct tggtctactc catgccctcc cggaacctgt   480
ccctgcgggt ggagggtctc caggagaaag actctggccc ctacagctgc tccgtgaatg   540
tgcaagacaa acaaggcaaa tctaggggcc acagcatcaa aaccttagaa ctcaatgtac   600
tggttcctcc agctcctcca tcctgccgtc tccagggtgt gccccatgtg gggcaaacg   660
tgaccctgag ctgccagtct ccaaggagta agcccgttgt ccaataccag tgggatcggc   720
agcttccatc cttccagact ttctttgcac cagcattaga tgtcatccgt gggtctttaa   780
gcctcaccaa cctttcgtct tccatggctg gagtctatgt ctgcaaggcc cacaatgagg   840
```

```
tgggcactgc ccaatgtaat gtgacgctgg aagtgagcac agggcctgga gctgcagtgg     900
ttgctgaagc tgttgtgggt accctggttg gactggggtt gctggctggg ctggtcctct     960
tgtaccaccg ccggggcaag gccctggagg agccagccaa tgatatcaag gaggatgcca    1020
ttgctccccg gaccctgccc tggcccaaga gctcagacac aatctccaag aatgggaccc    1080
tttcctctgt cacctccgca cgagccctcc ggccacccca tggccctccc aggcctggtg    1140
cattgacccc cacgcccagt ctatccagcc aggccctgcc ctcaccaaga catgcccacg    1200
acagatgggg cccaccctca accaatatcc cccatccctg gtggggtttt ttcctttggc    1260
tttgagccgc atgggtgctg ngcctgtgat ggngcctgcc cagagtcaag ctggctctct    1320
ggtatgatga ccccaccact cattggctaa aggatttggg gtctctcctt cctataaggg    1380
tcacctctag cacagaggcc tgagtcatgg gaaagagtca cactcctgac ccttagtact    1440
ctgcccccac ctctctttac tgtgggaaaa ccatctcagt aagacctaag tgtccaggag    1500
acagaaggag aagaggaagt ggatctggaa ttgggaggag cctccaccca cccctgactc    1560
ctccttatga agccagctgc tgaaattagc tactcaccaa gagtgagggg cagagacttc    1620
cagtcactga gtctcccagg ccccttgat ctgtacccca cccctatcta acaccaccct     1680
tggctcccac tccagctccc tgtattgata taacctgtca ggctggcttg gttaggtttt    1740
actggggcag aggataggga atctcttatt aaaactaaca tgaaatatgt gttgttttca    1800
tttgcaaatt taaataaaga tacataatgt ttgtatgaga taagaaaaaa aaaaaaaaag    1860
ggcggccgc                                                            1869
```

<210> 142
<211> 394
<212> PRT
<213> Mus musculus

<400> 142

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Met Ile Leu Gln Ala Gly Thr Pro Glu Thr Ser Leu Leu Arg Val Leu
1               5                   10                  15
Phe Leu Gly Leu Ser Thr Leu Ala Ala Phe Ser Arg Ala Gln Met Glu
            20                  25                  30
Leu His Val Pro Pro Gly Leu Asn Lys Leu Glu Ala Val Glu Gly Glu
        35                  40                  45
Glu Val Val Leu Pro Ala Trp Tyr Thr Met Ala Arg Glu Glu Ser Trp
    50                  55                  60
Ser His Pro Arg Glu Val Pro Ile Met Ile Trp Phe Leu Glu Gln Glu
65                  70                  75                  80
Gly Lys Glu Pro Asn Gln Val Leu Ser Tyr Ile Asn Gly Val Met Thr
                85                  90                  95
Asn Lys Pro Gly Thr Ala Leu Val His Ser Ile Ser Ser Arg Asn Val
            100                 105                 110
Ser Leu Arg Leu Gly Ala Leu Gln Glu Gly Asp Ser Gly Thr Tyr Arg
        115                 120                 125
Cys Ser Val Asn Val Gln Asn Asp Glu Gly Lys Ser Ile Gly His Ser
    130                 135                 140
Ile Lys Ser Ile Glu Leu Lys Val Leu Val Pro Pro Ala Pro Pro Ser
145                 150                 155                 160
Cys Ser Leu Gln Gly Val Pro Tyr Val Gly Thr Asn Val Thr Leu Asn
                165                 170                 175
Cys Lys Ser Pro Arg Ser Lys Pro Thr Ala Gln Tyr Gln Trp Glu Arg
            180                 185                 190
Leu Ala Pro Ser Ser Gln Val Phe Phe Gly Pro Ala Leu Asp Ala Val
        195                 200                 205
Arg Gly Ser Leu Lys Leu Thr Asn Leu Ser Ile Ala Met Ser Gly Val
    210                 215                 220
Tyr Val Cys Lys Ala Gln Asn Arg Val Gly Phe Ala Lys Cys Asn Val
225                 230                 235                 240
Thr Leu Asp Val Met Thr Gly Ser Lys Ala Ala Val Val Ala Gly Ala
                245                 250                 255
Val Val Gly Thr Phe Val Gly Leu Val Leu Ile Ala Gly Leu Val Leu
```

```
            260                     265                     270
Leu Tyr Gln Arg Arg Ser Lys Thr Leu Glu Glu Leu Ala Asn Asp Ile
        275                     280                     285
Lys Glu Asp Ala Ile Ala Pro Arg Thr Leu Pro Trp Thr Lys Gly Ser
    290                     295                     300
Asp Thr Ile Ser Lys Asn Gly Thr Leu Ser Ser Val Thr Ser Ala Arg
305                     310                     315                     320
Ala Leu Arg Pro Pro Lys Ala Ala Pro Pro Arg Pro Gly Thr Phe Thr
                325                     330                     335
Pro Thr Pro Ser Val Ser Ser Gln Ala Leu Ser Ser Pro Arg Leu Pro
            340                     345                     350
Arg Val Asp Glu Pro Pro Pro Gln Ala Val Ser Leu Thr Pro Gly Gly
        355                     360                     365
Val Ser Ser Ser Ala Leu Ser Arg Met Gly Ala Val Pro Val Met Val
    370                     375                     380
Pro Ala Gln Ser Gln Ala Gly Ser Leu Val
385                     390
```

<210> 143
<211> 1846
<212> DNA
<213> Mus musculus

<400> 143

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gtcgacccac gcgtccggtg cacattcggg ttgccgccgc tcacccacaa cacctgtaga      60
caccgtgtgt ccaactctcc ctgagtactc cgggccaagg agggccatga ttcttcaggc     120
tggaaccccc gagaccagct tgctgcgggt tttgttcctg ggactgagta cccttgctgc     180
cttctcccga gctcagatgg agttgcacgt gcccccgggc ctcaacaaat tggaagcggt     240
agagggagaa gaagtggtgc tccccgcctg gtacacgatg gcacgggagg agtcgtggtc     300
ccaccccccgg gaggtgccca tcatgatctg gttcttggaa caagaaggga aggaaccaaa     360
ccaggtgttg tcttacatta atggagtcat gacaaataaa cctggaacag ccctggtcca     420
ctctatctct tcacggaatg tgtccctgcg cctgggggca ctccaggagg gagactctgg     480
gacttaccgc tgttctgtca atgtgcagaa tgatgaaggc aaaagtatag gccacagcat     540
caaaagcata gagctcaaag tgctggttcc tccagctcct ccatcctgta gtttacaggg     600
tgtaccctat gtcgggacca atgtgaccct gaactgcaag tccccaagga gtaaacctac     660
tgctcagtac cagtgggaga ggctggcccc atcctcccag gtcttctttg gaccagcctt     720
agatgctgtt cgtggatctt taaagctcac taacctttcc attgccatgt ctggagtcta     780
tgtctgcaag gctcaaaaca gagtgggctt tgccaagtgc aacgtgacct tggacgtgat     840
gacagggtcc aaggctgcag tggtcgctgg agcagttgtg ggcacttttg ttgggttggt     900
gctgatagct gggctggtcc tgttgtacca gcgccggagc aagaccttgg aagagctggc     960
caatgatatc aaggaagatg ccattgctcc ccggaccttg ccttggacca aaggctcaga    1020
cacaatctcc aagaatggga cactttcttc ggtcacctca gcacgagctc tgcggccacc    1080
caaggctgct cctccaagac ctggcacatt tactcccaca cccagtgtct ctagccaggc    1140
cctgtcctca ccaagactgc ccagggtaga tgaacccccca cctcaggcag tgtccctgac    1200
cccaggtggg gtttcttctt ctgctctgag ccgcatgggt gctgtgcctg tgatggtgcc    1260
tgcacagagt caggctgggt ctcttgtgtg atagcccagg cactcattag ctacatctgg    1320
tatctgacct ttctgtaaag gtctccttgt ggcacagagg actcaatctt gggaggatgc    1380
ccacattcta gacctccagt cctttgctcc tacctccttc tattgttgga atactgggcc    1440
tcagtaagac taaaatctgg gtcaaaggac aaaaggagga aatggacctg aggtaggggg    1500
ttgggagtga ggaggcttca cttcctccct gcttctccct gaagccagat gaatgctgcg    1560
gaagatcggc taccctccaa gggctctgga ggagactgcc agtcagtgat gcccctggct    1620
ctgtgatctg tacaacaccc ttatctaatg ctgtcctttg ccgttcgctc catctccctg    1680
tattaatata acctgtcctg ctggcttggc tgggttttgt tgtagcaggg ggataggaaa    1740
gacattttaa aatctgactt gaaattgatg tttttgtttt tattttgcaa atttcaataa    1800
agatacatcg catttgcatg gaaaaaaaaa aaaaaagggc ggccgc                   1846
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<210> 144
<211> 394

<212> PRT
<213> Mus musculus

<400> 144
Met Ile Leu Gln Ala Gly Thr Pro Glu Thr Ser Leu Leu Arg Val Leu
1 5 10 15
Phe Leu Gly Leu Ser Thr Leu Ala Ala Phe Ser Arg Ala Gln Met Glu
20 25 30
Leu His Val Pro Pro Gly Leu Asn Lys Leu Glu Ala Val Glu Gly Glu
35 40 45
Glu Val Val Leu Pro Ala Trp Tyr Thr Met Ala Arg Glu Glu Ser Trp
50 55 60
Ser His Pro Arg Glu Val Pro Ile Leu Ile Trp Phe Leu Glu Gln Glu
65 70 75 80
Gly Lys Glu Pro Asn Gln Val Leu Ser Tyr Ile Asn Gly Val Met Thr
85 90 95
Asn Lys Pro Gly Thr Ala Leu Val His Ser Ile Ser Ser Arg Asn Val
100 105 110
Ser Leu Arg Leu Gly Ala Leu Gln Glu Gly Asp Ser Gly Thr Tyr Arg
115 120 125
Cys Ser Val Asn Val Gln Asn Asp Glu Gly Lys Ser Ile Gly His Ser
130 135 140
Ile Lys Ser Ile Glu Leu Lys Ala Leu Val Pro Pro Ala Pro Pro Ser
145 150 155 160
Cys Ser Leu Gln Gly Val Pro Tyr Val Gly Thr Asn Val Thr Leu Asn
165 170 175
Cys Lys Ser Pro Arg Ser Lys Pro Thr Ala Gln Tyr Gln Trp Glu Arg
180 185 190
Leu Ala Pro Ser Ser Gln Val Phe Phe Gly Pro Ala Leu Asp Ala Val
195 200 205
Arg Gly Ser Leu Lys Leu Thr Asn Leu Ser Ile Ala Met Ser Gly Val
210 215 220
Tyr Val Cys Lys Ala Gln Asn Arg Val Gly Phe Ala Lys Cys Asn Val
225 230 235 240
Thr Leu Asp Val Met Thr Gly Ser Lys Ala Ala Val Val Ala Gly Ala
245 250 255
Val Val Gly Thr Phe Val Gly Leu Val Leu Ile Ala Gly Leu Val Leu
260 265 270
Leu Tyr Gln Arg Arg Ser Lys Thr Leu Glu Glu Leu Ala Asn Asp Ile
275 280 285
Lys Glu Asp Ala Ile Ala Pro Arg Thr Leu Pro Trp Thr Lys Gly Ser
290 295 300
Asp Thr Ile Ser Lys Asn Gly Thr Leu Ser Ser Val Thr Ser Ala Arg
305 310 315 320
Ala Leu Arg Pro Pro Lys Ala Ala Pro Pro Arg Pro Gly Thr Phe Thr
325 330 335
Pro Thr Pro Ser Val Ser Ser Gln Ala Leu Ser Ser Pro Arg Leu Pro
340 345 350
Arg Val Asp Glu Pro Pro Pro Gln Ala Val Ser Leu Thr Pro Gly Gly
355 360 365
Val Ser Ser Ser Ala Leu Ser Arg Met Gly Ala Val Pro Val Met Val
370 375 380
Pro Ala Gln Ser Gln Ala Gly Ser Leu Val
385 390

<210> 145
<211> 1846
<212> DNA

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<213> Mus musculus

<400> 145
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caccgtgtgt ccaactctcc ctgagtactc cgggccaagg agggccatga ttcttcaggc    120
tggaaccccc gagaccagct tgctgcgggt tttgttcctg ggactgagta cccttgctgc    180
cttctcccga gctcagatgg agttgcacgt gcccccgggc ctcaacaaat tggaagcggt    240
agagggagaa gaagtggtgc tccccgcctg gtacacgatg gcacgggagg agtcgtggtc    300
ccacccccgg gaggtgccca tcctgatctg gttcttggaa caagaaggga aggaaccaaa    360
ccaggtgttg tcttacatta atggagtcat gacaaataaa cctggaacag ccctggtcca    420
ctctatctct tcacggaatg tgtccctgcg cctgggggca ctccaggagg gagactctgg    480
gacttaccgc tgttctgtca atgtgcagaa tgatgaaggc aaaagtatag gccacagcat    540
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gacattttaa aatctgactt gaaattgatg tttttgtttt tattttgcaa atttcaataa   1800
agatacatcg catttgcatg gaaaaaaaaa aaaaaagggc ggccgc                   1846

<210> 146
<211> 394
<212> PRT
<213> Mus musculus

<400> 146
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            20                  25                  30
Leu His Val Pro Pro Gly Leu Asn Lys Leu Glu Ala Val Glu Gly Glu
        35                  40                  45
Glu Val Val Leu Pro Ala Trp Tyr Thr Met Ala Arg Glu Glu Ser Trp
    50                  55                  60
Ser His Pro Arg Glu Val Pro Ile Leu Ile Trp Phe Leu Glu Gln Glu
65                  70                  75                  80
Gly Lys Glu Pro Asn Gln Val Leu Ser Tyr Ile Asn Gly Val Met Thr
                85                  90                  95
Asn Lys Pro Gly Thr Ala Leu Val His Ser Ile Ser Ser Arg Asn Val
            100                 105                 110
Ser Leu Arg Leu Gly Ala Leu Gln Glu Gly Asp Ser Gly Thr Tyr Arg
        115                 120                 125
Cys Ser Val Asn Val Gln Asn Asp Glu Gly Lys Ser Ile Gly His Ser
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    130                 135                 140
Ile Lys Ser Ile Glu Leu Lys Val Leu Val Pro Pro Ala Pro Pro Ser
145                 150                 155                 160
Cys Ser Leu Gln Gly Val Pro Tyr Val Gly Thr Asn Val Thr Leu Asn
                165                 170                 175
Cys Lys Ser Pro Arg Ser Lys Pro Thr Ala Gln Tyr Gln Trp Glu Arg
            180                 185                 190
Leu Val Pro Ser Ser Gln Val Phe Phe Gly Pro Ala Leu Asp Ala Val
        195                 200                 205
Arg Gly Ser Leu Lys Leu Thr Asn Leu Ser Ile Ala Met Ser Gly Val
    210                 215                 220
Tyr Val Cys Lys Ala Gln Asn Arg Val Gly Phe Ala Lys Cys Asn Val
225                 230                 235                 240
Thr Leu Asp Val Met Thr Gly Ser Lys Ala Ala Val Val Ala Gly Ala
                245                 250                 255
Val Val Gly Thr Phe Val Gly Leu Val Leu Ile Ala Gly Leu Val Leu
            260                 265                 270
Leu Tyr Gln Arg Arg Ser Lys Thr Leu Glu Glu Leu Ala Asn Asp Ile
        275                 280                 285
Lys Glu Asp Ala Ile Ala Pro Arg Thr Leu Pro Trp Thr Lys Gly Ser
    290                 295                 300
Asp Thr Ile Ser Lys Asn Gly Thr Leu Ser Ser Val Thr Ser Ala Arg
305                 310                 315                 320
Ala Leu Arg Pro Pro Lys Ala Ala Pro Pro Arg Pro Gly Thr Phe Thr
                325                 330                 335
Pro Thr Pro Ser Val Ser Ser Gln Ala Leu Ser Ser Pro Arg Leu Pro
            340                 345                 350
Arg Val Asp Glu Pro Pro Pro Gln Ala Val Ser Leu Thr Pro Gly Gly
        355                 360                 365
Val Ser Ser Ser Ala Leu Ser Arg Met Gly Ala Val Pro Val Met Val
    370                 375                 380
Pro Ala Gln Ser Gln Ala Gly Ser Leu Val
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<210> 147
<211> 1846
<212> DNA
<213> Mus musculus

<400> 147

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tggaaccccc gagaccagct tgctgcgggt tttgttcctg ggactgagta cccttgctgc     180
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agagggagaa gaagtggtgc tccccgcctg gtacacgatg gcacgggagg agtcgtggtc     300
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ccaggtgttg tcttacatta atggagtcat gacaaataaa cctggaacag ccctggtcca     420
ctctatctct tcacggaatg tgtccctgcg cctgggggca ctccaggagg gagactctgg     480
gacttaccgc tgttctgtca atgtgcagaa tgatgaaggc aaaagtatag gccacagcat     540
caaaagcata gagctcaaag tgctggttcc tccagctcct ccatcctgta gtttacaggg     600
tgtaccctat gtcgggacca atgtgaccct gaactgcaag tccccaagga gtaaacctac     660
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agatgctgtt cgtggatctt taaagctcac taacctttcc attgccatgt ctggagtcta     780
tgtctgcaag gctcaaaaca gagtgggctt tgccaagtgc aacgtgacct tggacgtgat     840
gacagggtcc aaggctgcag tggtcgctgg agcagttgtg ggcacttttg ttgggttggt     900
gctgatagct gggctggtcc tgttgtacca gcgccggagc aagaccttgg aagagctggc     960
caatgatatc aaggaagatg ccattgctcc ccggaccttg ccttggacca aaggctcaga    1020
cacaatctcc aagaatggga cactttcttc ggtcacctca gcacgagctc tgcggccacc    1080
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agatacatcg catttgcatg gaaaaaaaaa aaaaaagggc ggccgc 1846

<210> 148
<211> 394
<212> PRT
<213> Mus musculus

<400> 148
Met Ile Leu Gln Ala Gly Thr Pro Glu Thr Ser Leu Leu Arg Val Leu
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Phe Leu Gly Leu Ser Thr Leu Ala Ala Phe Ser Arg Ala Gln Met Glu
20 25 30
Leu His Val Pro Pro Gly Leu Asn Lys Leu Glu Ala Val Glu Gly Glu
35 40 45
Glu Val Val Leu Pro Ala Trp Tyr Thr Met Ala Arg Glu Glu Ser Trp
50 55 60
Ser His Pro Arg Glu Val Pro Ile Leu Ile Trp Phe Leu Glu Gln Glu
65 70 75 80
Gly Lys Glu Pro Asn Gln Val Leu Ser Tyr Ile Asn Gly Val Met Thr
85 90 95
Asn Lys Pro Gly Thr Ala Leu Val His Ser Ile Ser Ser Arg Asn Val
100 105 110
Ser Leu Arg Leu Gly Ala Leu Gln Glu Gly Asp Ser Gly Thr Tyr Arg
115 120 125
Cys Ser Val Asn Val Gln Asn Asp Glu Gly Lys Ser Ile Gly His Ser
130 135 140
Ile Lys Ser Ile Glu Leu Lys Val Leu Val Pro Pro Ala Pro Pro Ser
145 150 155 160
Cys Ser Leu Gln Gly Val Pro Tyr Val Gly Thr Asn Val Thr Leu Asn
165 170 175
Cys Lys Ser Pro Arg Ser Lys Pro Thr Ala Gln Tyr Gln Trp Glu Arg
180 185 190
Leu Ala Pro Ser Ser Gln Val Phe Phe Gly Pro Ala Leu Asp Ala Val
195 200 205
Arg Gly Ser Leu Lys Leu Thr Asn Leu Ser Ile Ala Met Ser Gly Val
210 215 220
Tyr Val Cys Lys Ala Gln Asn Arg Val Gly Phe Ala Lys Cys Asn Val
225 230 235 240
Thr Leu Asp Val Met Thr Gly Ser Lys Ala Ala Val Val Ala Gly Ala
245 250 255
Val Val Gly Thr Phe Val Gly Leu Val Leu Ile Ala Gly Leu Val Leu
260 265 270
Leu Tyr Gln Arg Arg Ser Lys Thr Leu Glu Glu Leu Ala Asn Asp Ile
275 280 285
Lys Glu Asp Ala Ile Ala Pro Arg Thr Leu Pro Trp Thr Lys Gly Ser
290 295 300

Asp Thr Ile Ser Lys Asn Gly Thr Leu Ser Ser Val Thr Ser Ala Arg
305 310 315 320
Ala Leu Arg Pro Pro Lys Ala Ala Pro Pro Arg Pro Gly Thr Phe Thr
325 330 335
Pro Thr Pro Ser Val Ser Ser Gln Ala Leu Ser Ser Pro Arg Leu Pro
340 345 350
Arg Val Asp Glu Pro Pro Pro Gln Ala Val Ser Leu Thr Pro Gly Gly
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Val Ser Ser Ser Val Leu Ser Arg Met Gly Ala Val Pro Val Met Val
370 375 380
Pro Ala Gln Ser Gln Ala Gly Ser Leu Val
385 390

<210> 149
<211> 1846
<212> DNA
<213> Mus musculus

<400> 149
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cttctcccga gctcagatgg agttgcacgt gcccccgggc ctcaacaaat tggaagcggt 240
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agatacatcg catttgcatg gaaaaaaaaa aaaaaagggc ggccgc 1846

<210> 150
<211> 245
<212> PRT
<213> Homo sapiens

<400> 150
Met Arg Leu Phe Val Arg Pro Ser Val Arg Pro Ala Met Ala Ala Pro

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Ser Pro Gly Ala His Gly Glu Leu Cys Arg Pro Phe Gly Glu Asp Asn
        35                  40                  45
Ser Ile Pro Glu Ser Cys Pro Asp Phe Cys Cys Gly Ser Cys Ser Ser
    50                  55                  60
Gln Tyr Cys Cys Ser Asp Val Leu Lys Lys Ile Gln Trp Asn Glu Glu
65                  70                  75                  80
Met Cys Pro Glu Pro Glu Ser Ser Arg Phe Ser Ala His Pro Glu Thr
                85                  90                  95
Pro Glu Gln Leu Gly Ser Val Leu Lys Tyr Gln Ser Ser Leu Asp Ser
            100                 105                 110
Asp Asn Met Pro Gly Phe Gly Ala Thr Val Ala Ile Gly Leu Thr Val
        115                 120                 125
Phe Val Val Phe Ile Ala Thr Ile Ile Val Cys Phe Thr Cys Ser Cys
    130                 135                 140
Cys Cys Leu Tyr Lys Met Cys Cys Arg Pro Arg Pro Val Val Ser Asn
145                 150                 155                 160
Thr Thr Thr Thr Thr Val Val His Thr Ala Tyr Pro Gln Pro Gln Pro
                165                 170                 175
Val Ala Pro Ser Tyr Pro Gly Pro Thr Tyr Gln Gly Tyr His Pro Met
            180                 185                 190
Pro Pro Gln Pro Gly Met Pro Ala Ala Pro Tyr Pro Thr Gln Tyr Pro
        195                 200                 205
Pro Pro Tyr Leu Ala Gln Pro Thr Gly Pro Pro Ala Tyr His Glu Thr
    210                 215                 220
Leu Ala Gly Ala Ser Gln Pro Pro Tyr Asn Pro Ala Tyr Met Asp Pro
225                 230                 235                 240
Pro Lys Ala Val Pro
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<210> 151
<211> 1801
<212> DNA
<213> Homo sapiens

<400> 151

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cagctatcct ggaccaacat accagggcta ccatcccatg cccccccagc caggaatgcc   660
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a 1801

<210> 152
<211> 245
<212> PRT
<213> Homo sapiens

<400> 152
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20 25 30
Ser Pro Gly Ala His Gly Glu Leu Cys Arg Pro Phe Gly Glu Asp Asn
35 40 45
Ser Ile Pro Glu Ser Cys Pro Asp Phe Cys Cys Gly Ser Cys Ser Ser
50 55 60
Gln Tyr Cys Cys Ser Asp Val Leu Lys Lys Ile Gln Trp Asn Glu Glu
65 70 75 80
Met Cys Pro Glu Pro Glu Ser Ser Arg Phe Ser Ala His Pro Glu Thr
85 90 95
Pro Glu Gln Leu Gly Ser Ala Leu Lys Tyr Gln Ser Ser Leu Asp Ser
100 105 110
Asp Asn Met Pro Gly Phe Gly Ala Thr Val Ala Ile Gly Leu Thr Val
115 120 125
Phe Val Val Phe Ile Ala Thr Ile Ile Val Cys Phe Thr Cys Ser Cys
130 135 140
Cys Cys Leu Tyr Lys Met Cys Cys Arg Pro Arg Pro Val Val Ser Asn
145 150 155 160
Thr Thr Thr Thr Thr Ala Val His Thr Ala Tyr Pro Gln Pro Gln Pro
165 170 175
Val Ala Pro Ser Tyr Pro Gly Pro Thr Tyr Gln Gly Tyr His Pro Met
180 185 190
Pro Pro Gln Pro Gly Met Pro Ala Ala Pro Tyr Pro Thr Gln Tyr Pro
195 200 205
Pro Pro Tyr Leu Ala Gln Pro Thr Gly Pro Pro Ala Tyr His Glu Thr
210 215 220
Leu Ala Gly Ala Ser Gln Pro Pro Tyr Asn Pro Ala Tyr Met Asp Pro
225 230 235 240
Pro Lys Ala Val Pro
245

<210> 153
<211> 1801
<212> DNA
<213> Homo sapiens

<400> 153
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a                                                                   1801
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<210> 154
<211> 245
<212> PRT
<213> Homo sapiens

<400> 154

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Ala Pro Ser Pro Trp Thr Leu Ser Leu Leu Leu Leu Leu Leu Leu Pro
            20                  25                  30
Ser Pro Gly Ala His Gly Glu Leu Cys Arg Pro Phe Gly Glu Asp Asn
        35                  40                  45
Ser Ile Pro Glu Ser Cys Pro Asp Phe Cys Cys Gly Ser Cys Ser Ser
    50                  55                  60
Gln Tyr Cys Cys Ser Asp Val Leu Lys Lys Ile Gln Trp Asn Glu Glu
65                  70                  75                  80
Met Cys Pro Glu Pro Glu Ser Ser Arg Phe Ser Ala His Pro Glu Thr
                85                  90                  95
Pro Glu Gln Leu Gly Ser Ala Leu Lys Tyr Gln Ser Ser Leu Asp Ser
            100                 105                 110
Asp Asn Met Pro Gly Phe Gly Ala Thr Val Ala Ile Gly Leu Thr Val
        115                 120                 125
Phe Val Val Phe Ile Ala Thr Ile Ile Val Cys Phe Thr Cys Ser Cys
    130                 135                 140
Cys Cys Leu Tyr Lys Met Cys Cys Arg Pro Arg Pro Val Val Ser Asn
145                 150                 155                 160
Thr Thr Thr Thr Thr Val Val His Thr Ala Tyr Pro Gln Pro Gln Pro
```

```
                165                     170                     175
Val Ala Pro Ser Tyr Pro Gly Pro Thr Tyr Gln Gly Tyr His Pro Met
            180                     185                     190
Pro Pro Gln Pro Gly Met Pro Ala Val Pro Tyr Pro Thr Gln Tyr Pro
        195                     200                     205
Pro Pro Tyr Leu Ala Gln Pro Thr Gly Pro Pro Ala Tyr His Glu Thr
    210                     215                     220
Leu Ala Gly Ala Ser Gln Pro Pro Tyr Asn Pro Ala Tyr Met Asp Pro
225                     230                     235                     240
Pro Lys Ala Val Pro
                245
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<210> 155
<211> 1801
<212> DNA
<213> Homo sapiens

<400> 155

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cttgatgcgt ctgtttgtcc gtccgtccgt ccgtcccgcc atggctgcgc cggcgccctc     120
tccgtggacc ctttcgctgc tgctgttgtt gctactgccg tctccgggtg cccatggcga     180
gctgtgcagg cccttcggtg aagacaattc gatcccagag tcctgtcctg acttctgttg     240
tggctcctgt tccagccaat actgctgctc tgacgtgctg aagaaaatcc agtggaatga     300
ggaaatgtgc cctgagccag agtccagcag attttccgcc caccccggaga caccagaaca     360
gctgggttca gcgctgaagt atcagtccag tcttgacagt gacaacatgc cagggttcgg     420
agcgaccgtg gccatcggcc tgaccgtctt cgtggtgttt atcgctacca tcattgtgtg     480
ctttacctgc tcctgctgct gtctatataa gatgtgctgc cgcccacgac ctgtcgtgtc     540
caacaccaca actactaccg tggttcacac cgcttaccct cagcctcaac ctgtggcccc     600
cagctatcct ggaccaacat accagggcta ccatcccatg cccccccagc caggaatgcc     660
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tcccccaaag gcagttccct gagcctgccc ccagcctctt tggctaacat ttgattatgt     840
catgtgtgtg tgagtgctat gcagagttct ttactgctgt ctgtggtgcg tgtgccttgt     900
ctagacatgt ggcttcctct gctgatgacc aggtaggcac aaatcttacc agtgctggtt     960
gggaccaatc tgttttcttc ctcacttgaa attgtaattt ctgaaatttc aagtaaatta    1020
aaaacaatag ggtaggaggt atttcccgct tcaccccaag gtgaccagcc atagcctgcc    1080
acacatagga gagcaagctt tttgtgggtc catgtcctgc tttggggagt agccagctag    1140
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cctcagtggc agtgggtcag tgactgatgt cagagcacac taggcagaga gccccgtccg    1260
tctccatcag ctgtctgtct ggacggtccc actgtctttc ctgggactat gtagagggcc    1320
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tatccagatg tgtgataatt ggtgaggttg aaatccttgg ttcctggaga acaggaaacc    1500
tgacctctga cagtccgttt cccttgacac cagcttcata gaatacctga ctcctgtact    1560
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gggggtggag agcctggatg gtagctctgg accagatgtg aatgcctcca tattccctgt    1680
tggttcctgt ttcactggct gttttagttt tgtgttaatt ggtgtttctg agcattcaaa    1740
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a                                                                    1801
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<210> 156
<211> 245
<212> PRT
<213> Homo sapiens

<400> 156

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1               5                   10                  15
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20 25 30
Ser Pro Gly Ala His Gly Glu Leu Cys Arg Pro Phe Gly Glu Asp Asn
35 40 45
Ser Ile Pro Glu Ser Cys Pro Asp Phe Cys Cys Gly Ser Cys Ser Ser
50 55 60
Gln Tyr Cys Cys Ser Asp Val Leu Lys Lys Ile Gln Trp Asn Glu Glu
65 70 75 80
Met Cys Pro Glu Pro Glu Ser Ser Arg Phe Ser Ala His Pro Glu Thr
85 90 95
Pro Glu Gln Leu Gly Ser Ala Leu Lys Tyr Gln Ser Ser Leu Asp Ser
100 105 110
Asp Asn Met Pro Gly Phe Gly Ala Thr Val Ala Ile Gly Leu Thr Val
115 120 125
Phe Val Val Phe Ile Ala Thr Ile Ile Val Cys Phe Thr Cys Ser Cys
130 135 140
Cys Cys Leu Tyr Lys Met Cys Cys Arg Pro Arg Pro Val Val Ser Asn
145 150 155 160
Thr Thr Thr Thr Thr Val Val His Thr Ala Tyr Pro Gln Pro Gln Pro
165 170 175
Val Ala Pro Ser Tyr Pro Gly Pro Thr Tyr Gln Gly Tyr His Pro Met
180 185 190
Pro Pro Gln Pro Gly Met Pro Ala Ala Pro Tyr Pro Thr Gln Tyr Pro
195 200 205
Pro Pro Tyr Leu Ala Gln Pro Thr Gly Pro Pro Ala Tyr His Glu Thr
210 215 220
Leu Ala Gly Ala Ser Gln Pro Pro Tyr Asn Pro Ala Tyr Met Asp Pro
225 230 235 240
Pro Lys Val Val Pro
245

<210> 157
<211> 1801
<212> DNA
<213> Homo sapiens

<400> 157
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tccgtggacc ctttcgctgc tgctgttgtt gctactgccg tctccgggtg cccatggcga 180
gctgtgcagg ccccttcggtg aagacaattc gatcccagag tcctgtcctg acttctgttg 240
tggctcctgt tccagccaat actgctgctc tgacgtgctg aagaaaatcc agtggaatga 300
ggaaatgtgc cctgagccag agtccagcag attttccgcc cacccggaga caccagaaca 360
gctgggttca gcgctgaagt atcagtccag tcttgacagt gacaacatgc cagggttcgg 420
agcgaccgtg gccatcggcc tgaccgtctt cgtggtgttt atcgctacca tcattgtgtg 480
ctttacctgc tcctgctgct gtctatataa gatgtgctgc cgcccacgac ctgtcgtgtc 540
caacaccaca actactaccg tggttcacac cgcttaccct cagcctcaac ctgtggcccc 600
cagctatcct ggaccaacat accagggcta ccatcccatg cccccccagc caggaatgcc 660
agcagcaccc tacccaacgc agtaccctcc accctacctg gcccagccca cagggccacc 720
agcctatcat gagacgttgg ctggagccag ccagcctcca tacaacccgg cctacatgga 780
tcccccaaag gtagttccct gagcctgccc ccagcctctt tggctaacat ttgattatgt 840
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tctccatcag ctgtctgtct ggacggtccc actgtctttc ctgggactat gtagagggcc    1320
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actctggttt ctccctacag tgtcttttta cgattagcca aacatattgc ctgtttttg     1440
tatccagatg tgtgataatt ggtgaggttg aaatccttgg ttcctggaga acaggaaacc    1500
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tggttcctgt ttcactggct gttttagttt tgtgttaatt ggtgtttctg agcattcaaa    1740
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a                                                                    1801
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<210> 158
<211> 213
<212> PRT
<213> Mus musculus

<400> 158

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            20                  25                  30
Gly Glu Asp Asn Ser Ile Pro Val Phe Cys Pro Asp Phe Cys Cys Gly
        35                  40                  45
Ser Cys Ser Asn Gln Tyr Cys Cys Ser Asp Val Leu Arg Lys Ile Gln
    50                  55                  60
Trp Asn Glu Glu Met Cys Pro Glu Pro Glu Ser Ser Arg Phe Ser Thr
65                  70                  75                  80
Pro Ala Glu Glu Thr Pro Glu His Leu Gly Ser Ala Leu Lys Phe Arg
                85                  90                  95
Ser Ser Phe Asp Ser Asp Pro Met Ser Gly Phe Gly Ala Thr Val Ala
            100                 105                 110
Ile Gly Val Thr Met Phe Val Val Phe Ile Ala Thr Ile Ile Ile Cys
        115                 120                 125
Phe Thr Cys Ser Cys Cys Cys Leu Tyr Lys Met Cys Cys Pro Gln Arg
    130                 135                 140
Pro Val Val Thr Asn Thr Thr Thr Thr Thr Val Val His Ala Pro Tyr
145                 150                 155                 160
Pro Gln Pro Gln Pro Gln Pro Val Ala Pro Ser Tyr Pro Gly Pro Thr
                165                 170                 175
Tyr Gln Gly Tyr His Pro Met Pro Pro Pro Ala Arg Asn Ala Ser Ser
            180                 185                 190
Thr Leu Pro Asn Ala Val Pro Thr Thr Leu Pro Gly Pro Ala His Arg
        195                 200                 205
Ala Ala Thr Leu Pro
    210
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<210> 159
<211> 1858
<212> DNA
<213> Mus musculus

<400> 159

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tgttcgtccg tccgttggtc tgtcccgcca tggctgcgcc ggcgccctct ctgtggaccc     120
tattgctgct gctgttgctg ctgccgccgc ctccgggtgc ccatggtgag ctgtgcaggc     180
cctttggtga agacaattcg atcccagtgt tctgtcctga tttctgttgt ggttcctgtt     240
ccaaccaata ctgctgctcg gacgtgctga ggaaaatcca gtggaatgag gaaatgtgtc     300
ctgagccaga gtccagcaga ttttccaccc ccgcggagga gacacccgaa catctgggtt     360
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cagcgctgaa atttcgatcc agttttgaca gtgaccctat gtcagggttc ggagcgaccg 420
tcgccattgg cgtgaccatg tttgtggtgt ttattgccac tatcatcatc tgcttcacct 480
gctcctgctg ctgtctgtat aagatgtgct gcccccaacg ccctgtcgtg accaacacca 540
caactactac cgtggttcat gccccttacc ctcagcctca acctcaacct gtggccccca 600
gctatcctgg accaacatac cagggctacc atcccatgcc ccccccagcc aggaatgcca 660
gcagcaccct acccaacgca gtacccacca ccctacctgg cccagcccac agggccgcca 720
ccctaccatg agtccttggc tggagccagc cagcctccat acaacccgac ctacatggat 780
tccctaaaga caattccctg aacctgcccc cagcctcttt ggctgccatt tatgtcgtgt 840
gtgagtgagt gatacgcaga gttctttact gctgtctgtg gtgtgtgtgc cttgtctaga 900
catgtggctt cctctgctgt tgaccaggta ggcgcaagtc ttaccagtgt gggtcgggac 960
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tgcaacattg gaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaagg gcggccgc 1858

<210> 160
<211> 213
<212> PRT
<213> Mus musculus

<400> 160
Met Ala Ala Pro Ala Pro Ser Leu Trp Thr Leu Leu Leu Leu Leu Leu
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Leu Leu Pro Pro Pro Pro Gly Ala His Gly Glu Leu Cys Arg Pro Phe
20 25 30
Gly Glu Asp Asn Ser Ile Pro Val Phe Cys Pro Asp Phe Cys Cys Gly
35 40 45
Ser Cys Ser Asn Gln Tyr Cys Cys Ser Asp Val Leu Arg Lys Ile Gln
50 55 60
Trp Asn Glu Glu Met Cys Pro Glu Pro Glu Ser Ser Arg Phe Ser Thr
65 70 75 80
Pro Ala Glu Glu Thr Pro Glu His Leu Gly Ser Ala Leu Lys Phe Arg
85 90 95
Ser Ser Phe Asp Ser Asp Pro Met Ser Gly Phe Gly Ala Thr Val Ala
100 105 110
Ile Gly Val Thr Ile Phe Val Val Phe Ile Val Thr Ile Ile Ile Cys
115 120 125
Phe Thr Cys Ser Cys Cys Cys Leu Tyr Lys Met Cys Cys Pro Gln Arg
130 135 140
Pro Val Val Thr Asn Thr Thr Thr Thr Thr Val Val His Ala Pro Tyr
145 150 155 160
Pro Gln Pro Gln Pro Gln Pro Val Ala Pro Ser Tyr Pro Gly Pro Thr
165 170 175
Tyr Gln Gly Tyr His Pro Met Pro Pro Pro Ala Arg Asn Ala Ser Ser
180 185 190
Thr Leu Pro Asn Ala Val Pro Thr Thr Leu Pro Gly Pro Ala His Arg
195 200 205

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Ala Ala Thr Leu Pro
    210

&lt;210&gt; 161
&lt;211&gt; 1858
&lt;212&gt; DNA
&lt;213&gt; Mus musculus

&lt;400&gt; 161
gtcgacccac gcgtccgcgc ggaggttgcg gcggcaccgt ggtcttgggc ttggtccgtc      60
tgttcgtccg tccgttggtc tgtcccgcca tggctgcgcc ggcgccctct ctgtggaccc     120
tattgctgct gctgttgctg ctgccgccgc ctccgggtgc ccatggtgag ctgtgcaggc     180
cctttggtga agacaattcg atcccagtgt tctgtcctga tttctgttgt ggttcctgtt     240
ccaaccaata ctgctgctcg gacgtgctga ggaaaatcca gtggaatgag gaaatgtgtc     300
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cagcgctgaa atttcgatcc agttttgaca gtgaccctat gtcagggttc ggagcgaccg     420
tcgccattgg cgtgaccatc tttgtggtgt ttattgtcac tatcatcatc tgcttcacct     480
gctcctgctg ctgtctgtat aagatgtgct gcccccaacg ccctgtcgtg accaacacca     540
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gcagcaccct acccaacgca gtacccacca ccctacctgg cccagcccac agggccgcca     720
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tagctttgtg ttgattggtg tttctgagca ttcagactcc gcaccctcat ttctaataaa    1800
tgcaacattg gaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaagg gcggccgc      1858

&lt;210&gt; 162
&lt;211&gt; 213
&lt;212&gt; PRT
&lt;213&gt; Mus musculus

&lt;400&gt; 162
Met Ala Ala Pro Ala Pro Ser Leu Trp Thr Leu Leu Leu Leu Leu Leu
1               5                   10                  15
Leu Leu Pro Pro Pro Pro Gly Ala His Gly Glu Leu Cys Arg Pro Phe
            20                  25                  30
Gly Glu Asp Asn Ser Ile Pro Val Phe Cys Pro Asp Phe Cys Cys Gly
        35                  40                  45
Ser Cys Ser Asn Gln Tyr Cys Cys Ser Asp Val Leu Arg Lys Ile Gln
    50                  55                  60
Trp Asn Glu Glu Met Cys Pro Glu Pro Glu Ser Ser Arg Phe Ser Thr
65                  70                  75                  80
Pro Ala Glu Glu Thr Pro Glu His Leu Gly Ser Ala Leu Lys Phe Arg
```

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                85                  90                  95
Ser Ser Phe Asp Ser Asp Pro Met Ser Gly Phe Gly Ala Thr Val Ala
            100                 105                 110
Ile Gly Val Thr Ile Phe Val Val Phe Ile Ala Thr Ile Ile Ile Cys
        115                 120                 125
Phe Thr Cys Ser Cys Cys Cys Leu Tyr Lys Met Cys Cys Pro Gln Arg
    130                 135                 140
Pro Val Val Thr Asn Thr Thr Thr Thr Thr Val Ala His Ala Pro Tyr
145                 150                 155                 160
Pro Gln Pro Gln Pro Gln Pro Val Ala Pro Ser Tyr Pro Gly Pro Thr
                165                 170                 175
Tyr Gln Gly Tyr His Pro Met Pro Pro Pro Ala Arg Asn Ala Ser Ser
            180                 185                 190
Thr Leu Pro Asn Ala Val Pro Thr Thr Leu Pro Gly Pro Ala His Arg
        195                 200                 205
Ala Ala Thr Leu Pro
    210
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<210> 163
<211> 1858
<212> DNA
<213> Mus musculus

<400> 163

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tattgctgct gctgttgctg ctgccgccgc ctccgggtgc ccatggtgag ctgtgcaggc    180
cctttggtga agacaattcg atcccagtgt tctgtcctga tttctgttgt ggttcctgtt    240
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tcgccattgg cgtgaccatc tttgtggtgt ttattgccac tatcatcatc tgcttcacct    480
gctcctgctg ctgtctgtat aagatgtgct gcccccaacg ccctgtcgtg accaacacca    540
caactactac cgtggctcat gccccttacc ctcagcctca acctcaacct gtggccccca    600
gctatcctgg accaacatac cagggctacc atcccatgcc ccccccagcc aggaatgcca    660
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catgtggctt cctctgctgt tgaccaggta ggcgcaagtc ttaccagtgt gggtcgggac    960
caacctgttt tcttcctcac ttgaaattgt actttctgaa atttcaagca aattaaaaac   1020
aataaggtag gaggtatttc ccacgtcacc ccaaggtgac cagccatggc ctgtcatact   1080
taggagagca agctttttgc gggtacagag caggctttgg ggggtaacca gctagctgct   1140
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caccaggtga caaggggact cagtggcagg gggtcacacc aggcagaaca ccatacactc   1260
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gacaccatct tcatagaaat acctgactcc tgtaccacag tccagtttgt cccagtagca   1620
gggacaccaa ggccaatggg ttatctggac caaaggtggg gtggagggcc tagatggtat   1680
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tagctttgtg ttgattggtg tttctgagca ttcagactcc gcaccctcat ttctaataaa   1800
tgcaacattg gaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaagg gcggccgc     1858
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<210> 164
<211> 213

<212> PRT
<213> Mus musculus

<400> 164
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Met Ala Ala Pro Ala Pro Ser Leu Trp Thr Leu Leu Leu Leu Leu Leu
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Leu Leu Pro Pro Pro Pro Gly Ala His Gly Glu Leu Cys Arg Pro Phe
            20                  25                  30
Gly Glu Asp Asn Ser Ile Pro Val Phe Cys Pro Asp Phe Cys Cys Gly
        35                  40                  45
Ser Cys Ser Asn Gln Tyr Cys Cys Ser Asp Val Leu Arg Lys Ile Gln
    50                  55                  60
Trp Asn Glu Glu Met Cys Pro Glu Pro Glu Ser Ser Arg Phe Ser Thr
65                  70                  75                  80
Pro Ala Glu Glu Thr Pro Glu His Leu Gly Ser Ala Leu Lys Phe Arg
                85                  90                  95
Ser Ser Phe Asp Ser Asp Pro Met Ser Gly Phe Gly Ala Thr Val Ala
            100                 105                 110
Ile Gly Val Thr Ile Phe Val Val Phe Ile Ala Thr Ile Ile Ile Cys
        115                 120                 125
Phe Thr Cys Ser Cys Cys Cys Leu Tyr Lys Met Cys Cys Pro Gln Arg
    130                 135                 140
Pro Val Val Thr Asn Thr Thr Thr Thr Thr Val Val His Ala Pro Tyr
145                 150                 155                 160
Pro Gln Pro Gln Pro Gln Pro Val Ala Pro Ser Tyr Pro Gly Pro Thr
                165                 170                 175
Tyr Gln Gly Tyr His Pro Met Pro Pro Pro Ala Arg Asn Ala Ser Ser
            180                 185                 190
Thr Leu Pro Asn Val Val Pro Thr Thr Leu Pro Gly Pro Ala His Arg
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<212> DNA
<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<212> DNA
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<213> Mus musculus

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<210> 181
<211> 1218
<212> DNA
<213> Mus musculus

<400> 181

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<210> 182
<211> 1110
<212> DNA
<213> Homo sapiens

<220>
<221> modified_base
<222> all "n" positions
<223> n=a, c, g, or t

<400> 182

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gaggatcagg tgttgtccta catcaatggg gtcacaacaa gcaaacctgg agtatccttg     300
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<210> 183
<211> 1110
<212> DNA
<213> Homo sapiens

<220>
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<222> all "n" positions
<223> n=a, c, g, or t

<400> 183
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<210> 184
<211> 1110
<212> DNA
<213> Homo sapiens

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<222> all "n" positions
<223> n=a, c, g, or t

<400> 184
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<210> 185
<211> 1110
<212> DNA
<213> Homo sapiens

<220>
<221> modified_base
<222> all "n" positions
<223> n=a, c, g, or t

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<210> 186
<211> 1182
<212> DNA
<213> Mus musculus

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aaattggaag cggtagaggg agaagaagtg gtgctccccg cctggtacac gatggcacgg 180

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<210> 187
<211> 1182
<212> DNA
<213> Mus musculus

<400> 187

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<210> 188
<211> 1182
<212> DNA
<213> Mus musculus

<400> 188

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aaattggaag cggtagaggg agaagaagtg gtgctccccg cctggtacac gatggcacgg     180
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<210> 189
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<213> Mus musculus

<400> 189

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/16883

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :C07K 14/47; C07H 21/04; C12N 15/63, 1/21; C12P 21/02
US CL : 530/350; 536/23.5; 435/320.1, 252.3, 361, 69.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/350; 536/23.5; 435/320.1, 252.3, 361, 69.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	WO 99/10492 A1 (ZYMOGENETICS, INC.) 04 March 1999 (04.03.99), see entire document, especially SEQ ID NOS: 1 and 2, page 4, line 16 to page 5, line 24, page 6, line 7 to page 8, line 17.	1-10 and 12 ----- 18
X	Database EST, National Cancer Institute, Cancer Genome Anatomy Project (CGAP), Tumor Gene Index, AN AI481222. 'vh21h07.x1 Soares_mammary_gland_NbMMG Mus musculus cDNA clone IMAGE:876157 3' similar to SW:CA28_HUMAN P25067 COLLAGEN ALPHA 2(VIII) CHAIN :, mRNA sequence'. 09 March 1999.	1, 3-5

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 SEPTEMBER 2000	22 SEP 2000

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Jayce Bridgers EILEEN B. O'HARA
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/16883

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
   1-10, 12 and 18

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

Commercial Sequence Databases: GenEmbl, N_Geneseq_36, Issued_Patents_NA, EST, a-geneseq36, swiss-prot38, strembl12, pir64, a-issued
Sequences searched: SEQ ID NOS: 1-3 and 8-10

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s)1-10, 12 and 18, in so far as they are drawn to human and mouse Tango 253, polynucleotides of SEQ ID NOS:1, 2, 8 and 9, vector, host cell, method of producing a protein and polypeptides of SEQ ID NOS:3-5 and 10-12.
Groups II-IV, claim(s) 1-10, 12 and 18, in so far as they are drawn to the polynucleotides of distinct cDNA clones and encoded proteins of human and mouse Intercept 258, Tango 281 and Tango 257, listed in Tables 1-4, pages 59-63.
Groups V-VIII, claim(s) 11 and 15, in so far as they are drawn to antibodies and binding compounds to the polypeptides listed in groups I-IV, respectively.
Groups IX-XII, claim(s) 13, 14, 19, 20 and 22, in so far as they are drawn to a method for detecting the presence of a polypeptide or a method for identifying a compound which binds to or modulates the activity of a polypeptide listed in groups I-IV, respectively.
Groups XIII-XVI, claim(s) 16 and 17, in so far as they are drawn to a method for detecting the presence of a nucleic acid molecule listed in groups I-IV, respectively.
Groups XVII-XX, claim 21, in so far as it is drawn to a method for modulating the activity of a polypeptide listed in groups I-IV, respectively.

The inventions listed as Groups I-XX do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Group I corresponds to the first invention wherein the first product is the polynucleotide and the first method of using is the method of making the protein. Note that there is no method of making the polynucleotide. The invention also includes the protein made. Each of groups II-IV does not share the same or corresponding special technical feature because each group is drawn to a different polynucleotide and encoded protein, and each of groups V-XX does not share the same or corresponding special technical feature because each group is drawn to different compounds or methods of using the four polynucleotides and encoded proteins. This Authority therefore considers that the several inventions do not share a special technical feature within the meaning of PCT Rule 13.2 and thus do not relate to a single general inventive concept within the meaning of PCT Rule 13.1.